



US009465041B2

(12) **United States Patent**
Hryhorenko et al.

(10) **Patent No.:** **US 9,465,041 B2**
(45) **Date of Patent:** ***Oct. 11, 2016**

(54) **ANTIBODIES TO PALIPERIDONE AND USE THEREOF**

(71) Applicants: **Ortho-Clinical Diagnostics, Inc.**,
Raritan, NJ (US); **Janssen**
Pharmaceutical NV, Beerse (BE)

(72) Inventors: **Eric Hryhorenko**, Hilton, NY (US);
Banumathi Sankaran, Pittsford, NY
(US); **Thomas R. DeCory**, Pittsford,
NY (US); **Theresa Tubbs**, Rochester,
NY (US); **Linda Colt**, Rochester, NY
(US); **Maarten Vliegen**, Rijkersvael
(BE); **Pieter Rik Haspeslagh**, Halen
(BE)

(73) Assignee: **Janssen Pharmaceutica NV**, Beerse
(BE)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 193 days.

This patent is subject to a terminal dis-
claimer.

(21) Appl. No.: **13/971,416**

(22) Filed: **Aug. 20, 2013**

(65) **Prior Publication Data**

US 2014/0057298 A1 Feb. 27, 2014

Related U.S. Application Data

(60) Provisional application No. 61/691,692, filed on Aug.
21, 2012.

(51) **Int. Cl.**

G01N 33/94 (2006.01)

C07K 16/44 (2006.01)

(52) **U.S. Cl.**

CPC **G01N 33/9406** (2013.01); **C07K 16/44**
(2013.01); **G01N 33/9413** (2013.01); **C07K**
2317/56 (2013.01); **C07K 2317/565** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,166,452 A 9/1979 Generales, Jr.
5,120,643 A 6/1992 Ching et al.
5,559,041 A 9/1996 Kang et al.
5,587,458 A 12/1996 King et al.
5,642,870 A 7/1997 Sargis
5,714,389 A 2/1998 Charlton et al.
5,761,894 A 6/1998 Evans
6,034,078 A 3/2000 Fairhurst et al.
6,139,800 A 10/2000 Chandler
6,228,660 B1 5/2001 May et al.
7,163,681 B2 1/2007 Giles-Komar et al.
7,416,700 B2 8/2008 Buechler et al.
7,772,240 B2 8/2010 Bang-Andersen et al.
7,901,949 B2 3/2011 Raj

8,058,405 B2 11/2011 Demuth et al.
8,088,594 B2 1/2012 Salamone et al.
2003/0087306 A1 5/2003 Christensen et al.
2003/0143233 A1 7/2003 Goshorn et al.
2003/0202975 A1 10/2003 Tedder
2004/0127489 A1 7/2004 Pickar et al.
2005/0163708 A1 7/2005 Robinson et al.
2006/0046967 A1 3/2006 Satyam
2006/0235005 A1 10/2006 Goff
2006/0251592 A1 11/2006 Hendler et al.
2006/0289787 A1 12/2006 Ohman et al.
2007/0015290 A1 1/2007 Raj
2007/0231883 A1 10/2007 Lindstrom et al.
2008/0260812 A1 10/2008 Matsuyama et al.
2009/0325193 A1 12/2009 Grenier et al.
2010/0069356 A1 3/2010 Gant et al.
2010/0111852 A1 5/2010 Yoshida
2010/0144781 A1 6/2010 Fu et al.
2010/0166502 A1 7/2010 DeMay
2010/0203129 A1 8/2010 Andersen et al.
2010/0266502 A1 10/2010 Kimura
2011/0229979 A1 9/2011 Salamone et al.
2011/0230520 A1 9/2011 Sartor et al.
2011/0245224 A1 10/2011 Barvian et al.
2012/0004165 A1 1/2012 Keil et al.
2012/0071636 A1 3/2012 Salamone et al.
2014/0057302 A1* 2/2014 Hryhorenko G01N 33/94
435/7.93

FOREIGN PATENT DOCUMENTS

EP 0582368 B1 1/2001
EP 0583820 B1 3/2002
EP 2316468 A1 5/2011
EP 2343296 A1 7/2011
WO WO 95/34652 A1 12/1995
WO WO 96/38442 A1 12/1996
WO WO 03/082877 A1 10/2003
WO WO 03/103835 A1 12/2003

(Continued)

OTHER PUBLICATIONS

Rudikoff et al. Single amino acid substitution altering antigen-
binding specificity. PNAS 1982, vol. 79, pp. 1979-1983.*

(Continued)

Primary Examiner — Shafiqul Haq

(74) *Attorney, Agent, or Firm* — Robert DeBarardine;
Johnson & Johnson

(57) **ABSTRACT**

Disclosed is an antibody which binds to paliperidone, which
can be used to detect paliperidone in a sample such as in a
competitive immunoassay method. The antibody can be
used in a lateral flow assay device for point-of-care detection
of paliperidone, including multiplex detection of aripipra-
zole, quetiapine, olanzapine, and risperidone/paliperidone in
a single lateral flow assay device.

18 Claims, 22 Drawing Sheets

(56)

References Cited

FOREIGN PATENT DOCUMENTS

WO	WO 2004/014895	A1	2/2004
WO	WO 2005/000901	A2	1/2005
WO	WO 2005/028458	A1	3/2005
WO	WO 2005/033073	A2	4/2005
WO	WO 2005/089082	A2	9/2005
WO	WO 2005/118139	A1	12/2005
WO	WO 2006/137785	A1	12/2006
WO	WO 2009/040409	A1	4/2009
WO	WO 2010/015029	A1	2/2010
WO	WO 2010/104749	A2	9/2010
WO	WO-2010/151711	A1	12/2010
WO	WO-2011/012715	A1	2/2011
WO	WO-2011/042450	A1	4/2011
WO	WO 2011/082076	A1	7/2011
WO	WO 2011/112657	A1	9/2011
WO	WO 2011/115733	A1	9/2011
WO	WO 2011/159537	A2	12/2011
WO	WO-2011/163594	A2	12/2011
WO	WO 2012/003418	A2	1/2012
WO	WO 2012/012595	A2	1/2012
WO	WO 2013/011407	A1	1/2013
WO	WO-2013/024047	A1	2/2013
WO	WO-2013/024048	A1	2/2013
WO	WO 2013/088255	A1	6/2013
WO	WO2014/031584-ISR		2/2014

OTHER PUBLICATIONS

Amit et al. Three-dimensional structure of an antigen-antibody complex at 2.8Å resolution. *Science* 1986, vol. 233, No. 4765, pp. 747-753.*

International Search Report for corresponding Application No. PCT/US2013/055700 mailed Oct. 10, 2013.

International Search Report for corresponding Application No. PCT/US2013/055712.

International Search Report for corresponding Application No. PCT/US2013/055724 mailed Sep. 24, 2013.

International Search Report for corresponding Application No. PCT/US2013/055729 dated Oct. 31, 2013.

International Search Report mailed Jan. 16, 2014 for Application No. PCT/US2013/55733.

International Search Report mailed Mar. 13, 2014 for Application No. PCT/US2013/55775.

International Search Report mailed Jan. 16, 2014 for Application No. PCT/US2013/55780.

International Search Report mailed Mar. 10, 2014 for Application No. PCT/US2013/55787.

International Search Report mailed Jan. 16, 2014 for Application No.

International Search Report mailed Mar. 10, 2014 for Application No. PCT/US2013/55803.

International Search Report mailed Jan. 30, 2014 for Application No. PCT/US2013/55817.

International Search Report mailed Mar. 3, 2014 for Application No. PCT/US2013/55826.

International Search Report mailed Jan. 16, 2014 for Application No. PCT/US2013/55830.

International Search Report mailed Mar. 4, 2014 for Application No. PCT/US2013/55834.

International Search Report mailed Oct. 31, 2013 for Application No. PCT/US2013/055282.

International Search Report mailed Oct. 11, 2013 for Application No. PCT/US2013/055263.

U.S. Appl. No. 13/971,387, filed Aug. 20, 2013.

U.S. Appl. No. 13/971,416, filed Aug. 20, 2013.

U.S. Appl. No. 13/971,429, filed Aug. 20, 2013.

U.S. Appl. No. 13/971,448, filed Aug. 20, 2013.

U.S. Appl. No. 13/971,475, filed Aug. 20, 2013.

U.S. Appl. No. 13/071,499, filed Aug. 20, 2013.

U.S. Appl. No. 13/971,519, filed Aug. 20, 2013.

U.S. Appl. No. 13/971,536, filed Aug. 20, 2013.

U.S. Appl. No. 13/971,546, filed Aug. 20, 2013.

U.S. Appl. No. 13/971,562, filed Aug. 20, 2013.

U.S. Appl. No. 13/970,650, filed Aug. 20, 2013.

U.S. Appl. No. 13/970,653, filed Aug. 20, 2013.

U.S. Appl. No. 13/970,660, filed Aug. 20, 2013.

U.S. Appl. No. 13/970,667, filed Aug. 20, 2013.

U.S. Appl. No. 13/970,673, filed Aug. 20, 2013.

U.S. Appl. No. 13/968,465, filed Aug. 20, 2013.

U.S. Appl. No. 13/968,480, filed Aug. 20, 2013.

Abdel-Baki, A., et al., "Pharmacotherapy Challenges in Patients with First-Episode Psychosis, *Journal of Affective Disorders*", vol. 138, pp. S3-S14 (2012).

Aliouane, L., et al., "Synthesis of Difluoromethylphosphonamides by Directed Addition of Amine", *Tetrahedron Letters*, vol. 52, pp. 3681-3685 (2011).

Annunziato, M., et al., "p-Maleimidophenyl Isocyanate: A Novel Heterobifunctional Linker for Hydroxyl to Thiol Coupling", *Bioconjugate Chemistry*, vol. 4, pp. 212-218 (1993).

Billah, Md., et al., "Directed Immobilization of Reduced Antibody Fragments onto a Novel SAM on Gold for Myoglobin Impedance Immunosensing", *Bioelectrochemistry*, vol. 80, pp. 49-54 (2010).

Bodin, A., et al., "Identification and Allergenic Activity of Hydroxyaldehydes-A New Type of Oxidation Product from an Ethylated Non-Ionic Surfactant", *Contact Dermatitis*, vol. 44, pp. 207-212 (2001).

Brinkley, Michael, "A Brief Survey of Methods for Preparing Protein Conjugates with Dyes, Haptens, and Cross-Linking Reagents", *Bioconjugate Chemistry*, vol. 3, pp. 2-13 (1992).

Carter, P., et al., "High Level *Escherichia Coli* Expression and Production of a Bivalent Humanized Antibody Fragment", *Biotechnology*, vol. 10, pp. 163-167.

Chamow, S., et al., "Conjugation of Soluble CD4 without Loss of Biological Activity via a Novel Carbohydrate-Directed Cross-Linking Reagent", *The Journal of Biological Chemistry*, vol. 267, No. 22, Issue of Aug. 5, pp. 15916-15922 (1992).

Chappey, O., et al., "Monoclonal Antibodies in Hapten Immunoassays", *Pharmaceutical Research*, vol. 9, No. 11, pp. 1375-1379 (1992).

Cleland, W. W., "Dithiothreitol, a New Protective Reagent for SH Groups", *Biochemistry*, vol. 3, No. 4, pp. 480-482 (1964).

Dai, R., et al., "A High-Throughput Assay for Evaluating State Dependence and Subtype Selectivity of Cav2 Calcium Channel Inhibitors", *Assay and Drug Development Technologies*, vol. 6, No. 2, pp. 195-212 (2008).

Danilova, N., et al., "Production and Characterization of Anti-Theophylline Monoclonal Antibodies Suitable for Immunoassay", *Immunology Letters*, vol. 29, pp. 79-84 (1991).

Davis, P., et al., "Development and Validation of an LC-MS/MS Method for the Determination of Quetiapine and Four Related Metabolites in Human Plasma", *Journal of Pharmaceutical and Biomedical Analysis*, vol. 51, pp. 1113-1119 (2010).

Diago-Meseguer, J., et al., "A New Reagent for Activating Carboxyl Groups, Preparation and Reactions of N,N-Bis[2-oxo-3-ox-azolidinyl]phosphorodiamidic Chloride", *Syntheses*, vol. 7(1), pp. 547-551 (1980).

Dixon, W.J., "Efficient Analysis of Experimental Observations", *Ann. Rev. Pharmacol. Toxicol.*, vol. 20, pp. 441-462 (1980).

Fiedler, H., et al., "Surface Chemical Characterization of Maleic Acid Mono[2-4-alkylpiperazinyl]ethyl esters. 1. The Complex Adsorption Behavior of an Ampholytic Surfactant", *Langmuir*, vol. 10, pp. 3959-3965 (1994).

Finley, F., et al., "An Integrated Multiassay Approach to the Discovery of Small-Molecule N-Type Voltage-Gated Calcium Channel Antagonists", *Assay and Drug Development Technologies*, vol. 8, No. 6, pp. 685-694 (2010).

Gentaur Molecular Products, Data Sheet, Enzyme Immunoassay for the Detection of Olanzapine in Urine or Serum, p. 2 (May 2012).

Ghetie, V., et al., "Preparation and Characterization of Conjugates of Recombinant CD4 and Deglycosylated Ricin a Chain Using Different Cross-Linkers", *Bioconjugate Chemistry*, vol. 1, pp. 24-31 (1990).

(56)

References Cited

OTHER PUBLICATIONS

Gorja, D., et al., "Novel N-Indolylmethyl Substituted Olanzapine Derivatives: Their Design, Synthesis and Evaluation as PDE4B Inhibitors+", *Organic & Biomolecular Chemistry*, vol. 11, pp. 2075-2079 (2013).

Heykants, J., et al., "The Pharmacokinetics of Risperidone in Humans: A Summary", *J. Clinical Psychiatry*, vol. 55(5), pp. 13-17 (1994).

Huang, M-L, et al., "Pharmacokinetics of the Novel Antipsychotic Agent Risperidone and the Prolactin Response in Healthy Subjects", *Clinical Pharmacology Therapeutics*, vol. 54, pp. 257-268 (1993).

Huse, W., et al., "Generation of a Large Combinatorial Library of the Immunoglobulin Repertoire in Phage Lambda", *Research Article*, pp. 1275-1281 (Dec. 1989).

Kim, S., et al., "An Experimental Model for Peripheral Neuropathy Produced by Segmental Spinal Nerve Ligation in the Rat", *Pain*, vol. 50, pp. 355-363 (1992).

Kirley, Terence L, "Reduction and Fluorescent Labeling of Cystine-Containing Proteins for Subsequent Structural Analyses", *Analytical Biochemistry*, vol. 180, pp. 231-236 (1989).

Kohler, C., et al., "Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity", *Nature*, vol. 256, Aug. 7 (1975) pp. 495-497.

Konig, W., et al., "A New Method for Synthesizing Peptides: Activation of Carboxyl Molecules With Dicyclohexylcarbodiimide by Adding 1-Hydroxybenzotriazoles", *Chem. Ber.* vol. 103, pp. 788-798 (1970).

Li, Z., et al., "Synthesis and Characterization of N-Benzoyl-N'-Carboxyalkyl Substituted Thiourea Derivatives", *Phosphorus, Sulfur and Silicon*, vol. 178, pp. 293-297 (2003).

Lieberman, J., et al., "Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia", *The New England Journal of Medicine*, vol. 353, pp. 1209-1223 (2005).

Liu, H., et al., "Organophosphorus Compound DEPBT as a Coupling Reagent for Oligopeptides and Peptides Synthesis: Studies on Its Mechanism", *Chinese Chemical Letters*, vol. 13, No. 7, pp. 601-604 (2002).

Maddox, D., et al., "Elevated Serum Levels in Human Pregnancy of a Molecule Immunochemically Similar to Eosinophil Granule major Basic Protein", *J. Exp. Medicine*, vol. 158, pp. 1211-1226 (1983).

Malachowski, W., et al. "The Chemistry of Phosphopeptides: Formation of Functionalized Phosphonochloridates Under Mild Conditions and Their Reaction With Alcohols and Amines", *Journal of Organic Chemistry*, vol. 59, pp. 7616-7624 (1994).

Modena, D., et al. "Production and Characterization of Murine Monoclonal Antibodies to Polypeptide Hormones and Their Fragments", *Annali Dell'Istituto Superiore di Sanita*, vol. 27, No. 1, pp. 167-174 (1991).

Needleman, S., et al., "A General Method Applicable to the Search for Similarities in the Amino Acid Sequence of Two Proteins", *J. Molecular Biology*, vol. 48, pp. 443-453 (1970).

Nielsen, C., et al., "Anti-Allodynic Efficacy of the α -Conopeptide, Xen2174, in Rats with Neuropathic Pain", *Pain*, vol. 118, p. 112-124 (2005).

Nolli, M., et al., "Antibodies Against the Antibiotics: An Overview", *Annali, Istituto Superiore di Sanita*, vol. 27, No. 1, pp. 149-154 (1991).

Park, J., et al., "Novel Cyanine Dyes with Vinylsulfone Group for Labeling Biomolecules", *Bioconjugate Chemistry*, pp. 350-362 (2012).

Penning, T., et al., "Synthesis of Potent Leukotriene A_4 Hydrolase Inhibitors. Identification of 3-[Methyl]4-(phenylmethyl)phenoxypropylamino]propanoic Acid", *J. Medical Chemistry*, vol. 45, pp. 3482-3490 (2002).

Pruhs, S., et al., "Upscaling the Solid-Phase Synthesis of a Tetrahydrocarabazole in Chemical Development" *Organic Process Research & Development*, vol. 10, pp. 441-445 (2006).

Schmid, K., et al., "Distribution of Cyclopropenoid Fatty Acids in Malvaceous Plant Parts", *Phytochemistry*, vol. 27, No. 9, pp. 2831-2834 (1988).

Smith, T., et al., "Comparison of Biosequences", *Advances in Applied Mathematics*, vol. 2, pp. 482-489 (1981).

Su, J., et al., "Modification of the Clozapine structure by Parallel Synthesis", *Bioorganic & Medicinal Chemistry Letters*, vol. 16, p. 4548-4553 (2006).

Subasinghe, N., et al., "A Novel Series of Pyrazolylpiperidine N-Type Calcium Channel Blockers", *Bioorganic & Medicinal Chemistry Letters*, vol. 22, pp. 4080-4083 (2012).

Van Os, J., et al., "Schizophrenia", *Lancet*, vol. 374, pp. 635-645 (2009).

Wilbur, D., et al., "Reagents for Astatination of Biomolecules; Comparison of the In Vivo Distribution and Stability of Some Radioiodinated/Astatinated Benzamidyl and *nido*-Carboranyl Compounds", *Bioconjugate Chemistry*, vol. 15, pp. 203-223 (2004).

Woestenborghs, R., et al., "On the Selectivity of Some Recently Developed RIA's", *Methodological Surveys in Biochemistry and Analysis*, vol. 20, pp. 241-246 (1990).

Wu, X., et al. "A New Homobifunctional *p*-Nitro Phenyl Ester X-Coupling Reagent for the Preparation of Neoglycoproteins", *Organic Letters*, vol. 6, No. 24, pp. 4407-4410 (2004).

Alphs et al., "Onset of efficacy with acute long-acting injectable paliperidone palmitate treatment in markedly to severely ill patients with schizophrenia: post hoc analysis of a randomized, double-blind clinical trial," *Annals of General Psychiatry*, 2011, 10(12): 1-10.

Spina, Edoardo, et al., "The Pharmacology and safety of paliperidone extended-release in the treatment of schizophrenia", *Expert Opinion on Drug Safety*, 2007; 6(6):651-662.

* cited by examiner

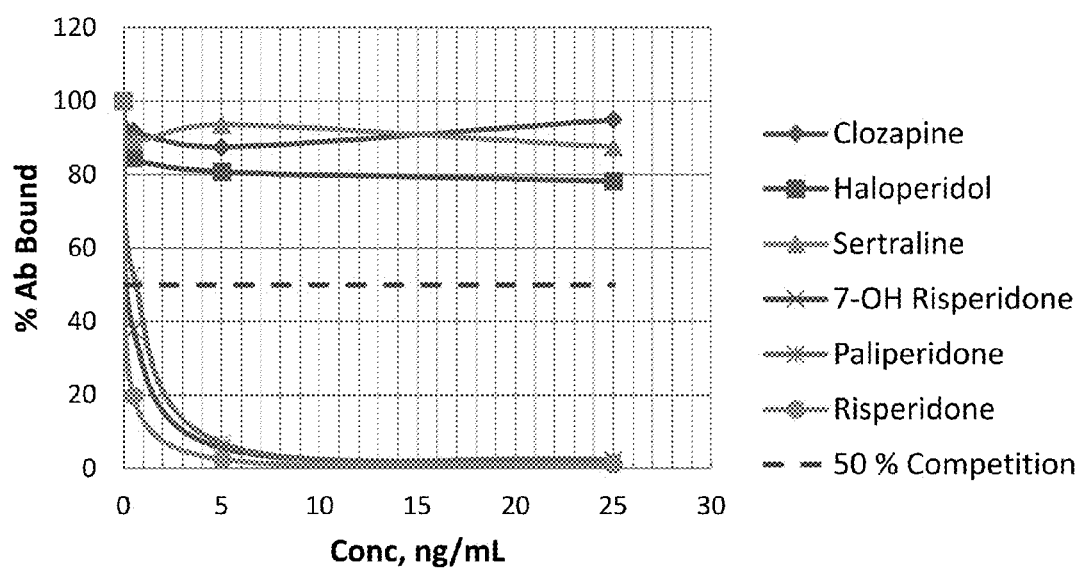
Fig. 1**CTI Mouse 2.2 subclone 5_9
Competition**

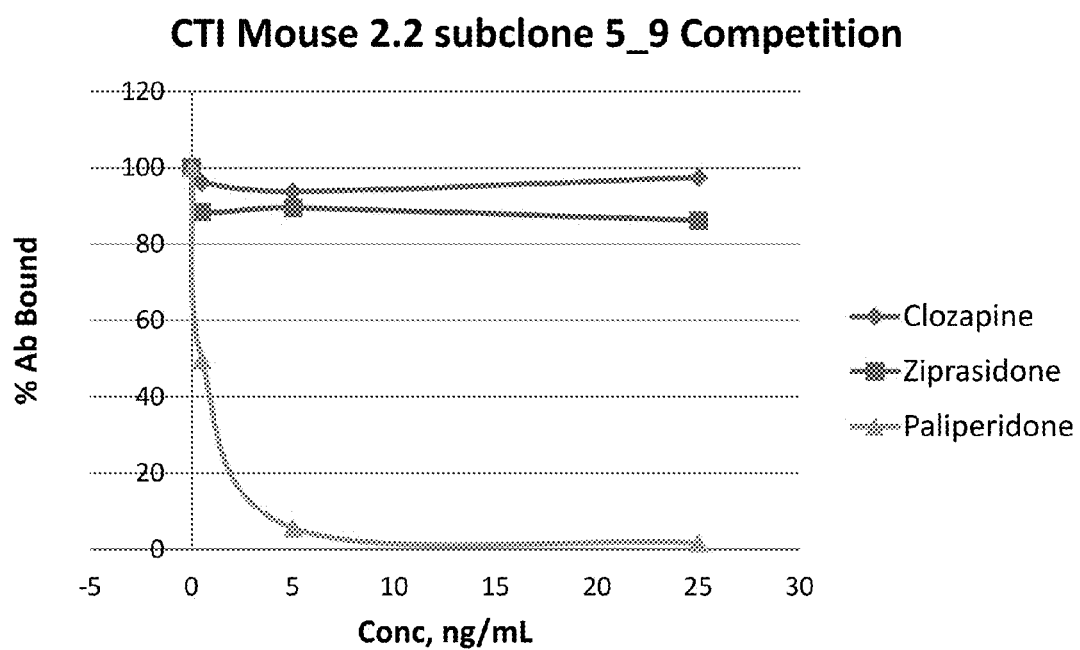
Fig. 2

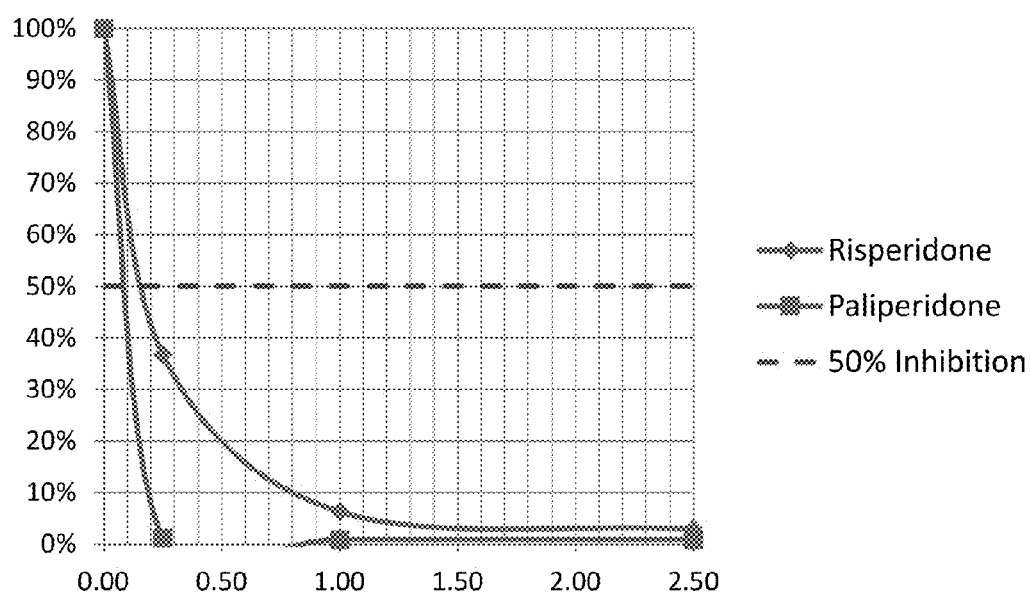
Fig. 3

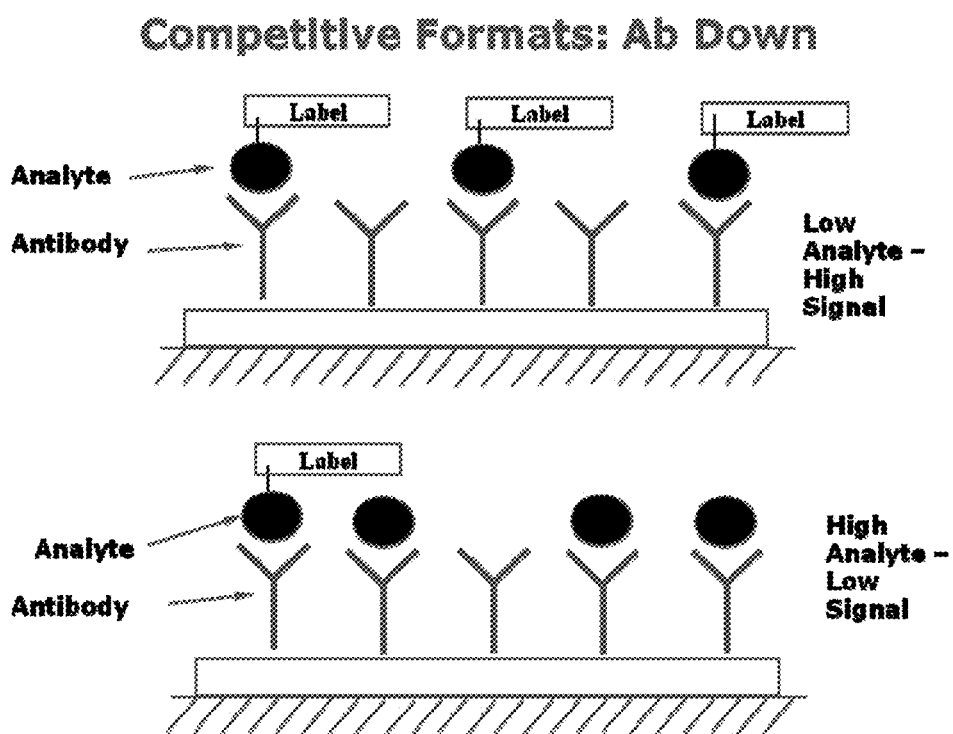
Fig. 4

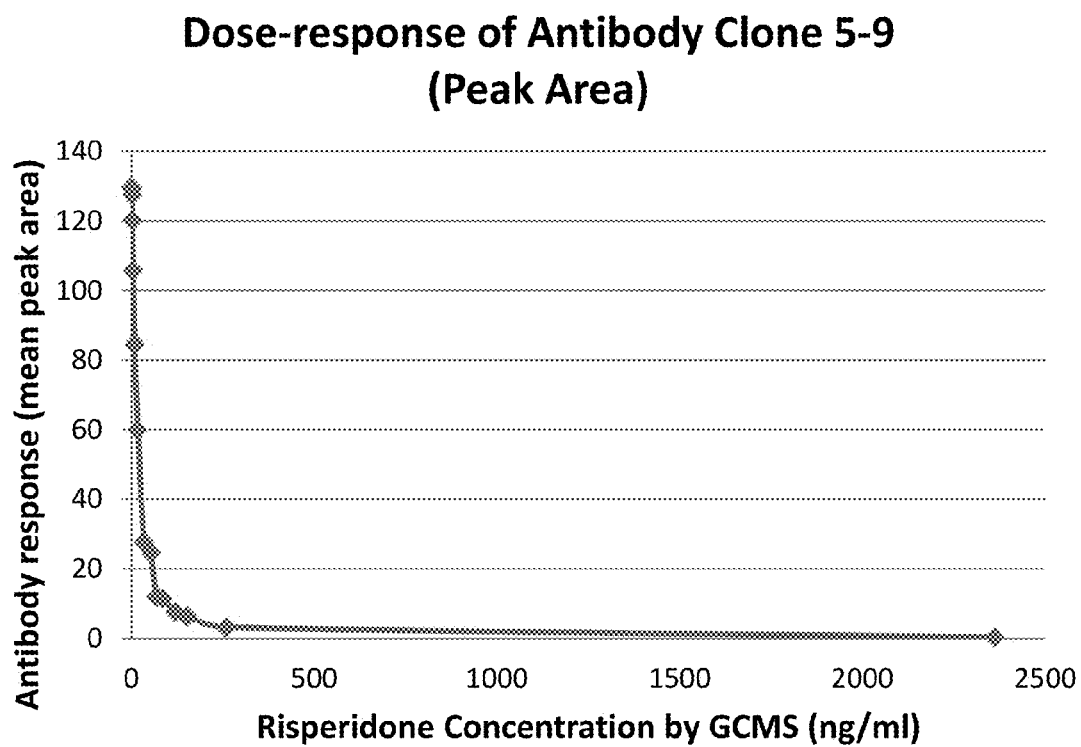
Fig. 5

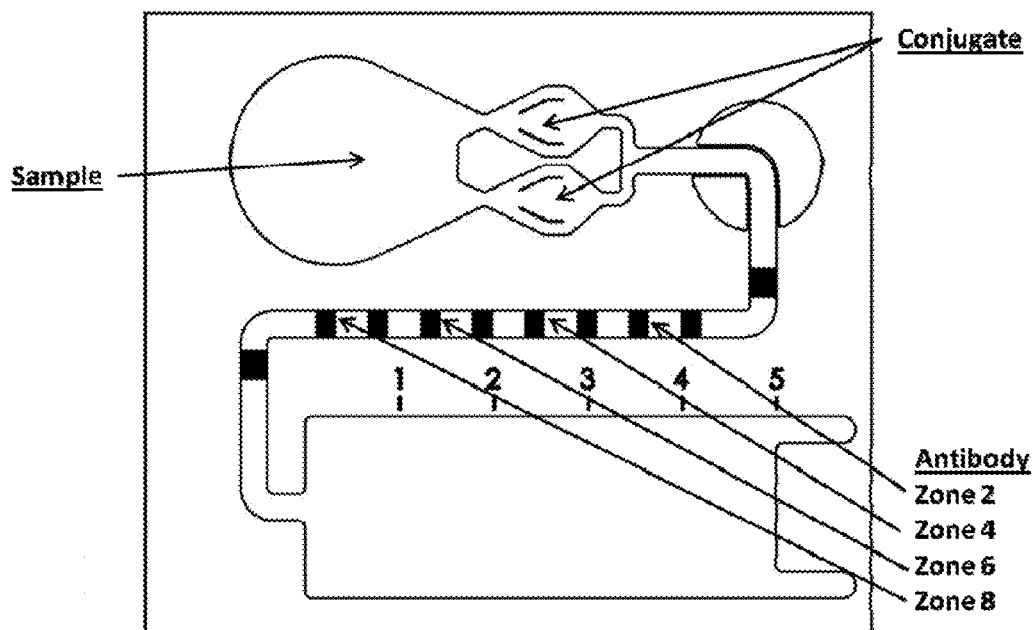
Fig. 6

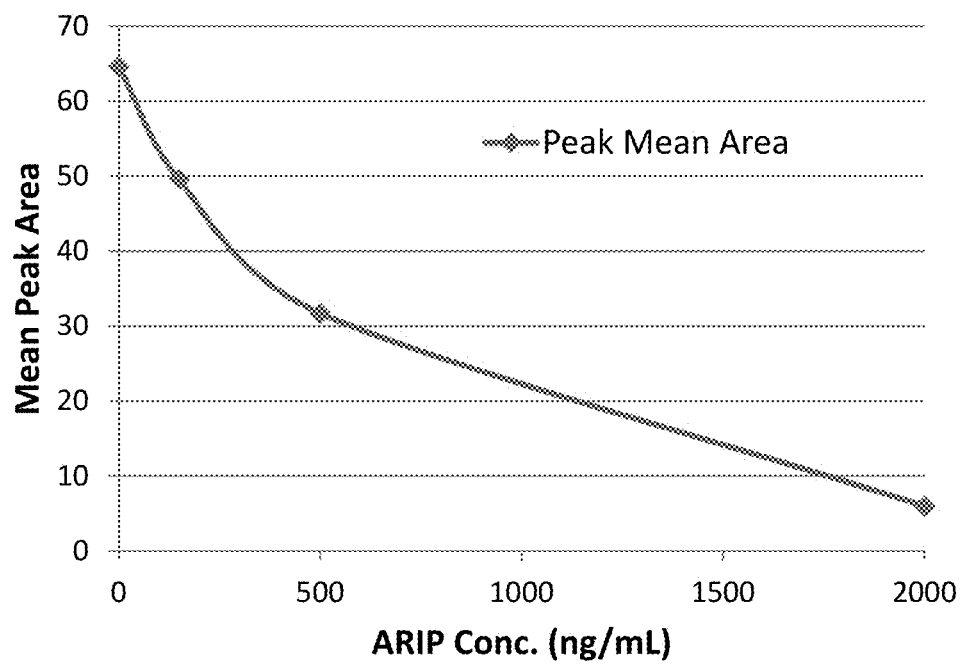
Fig. 7**ARIP Peak Mean Area vs. Conc.
Clone 5C7**

Fig. 8

**OLAN Peak Mean Area vs. Conc.
Clone 4G9-1**

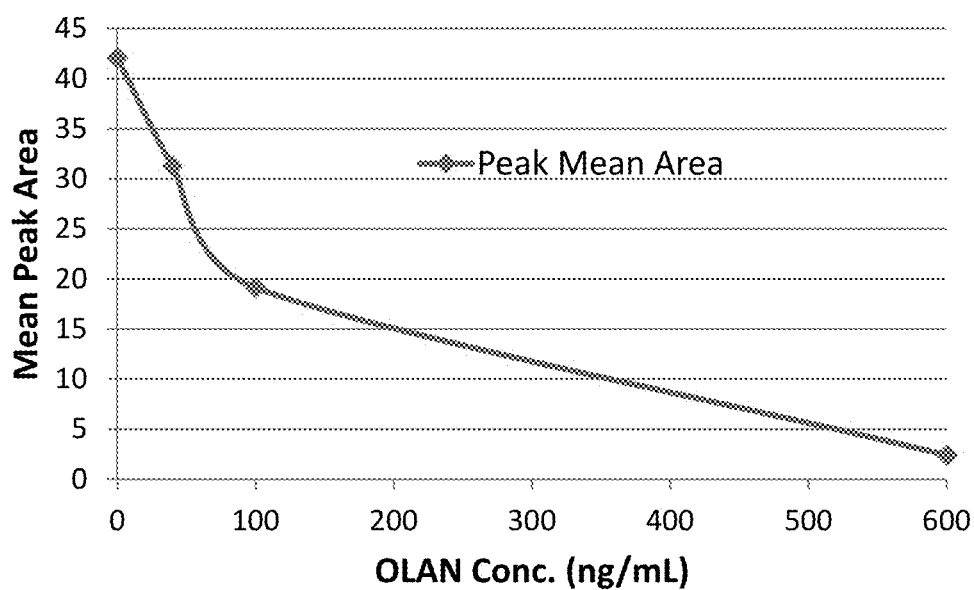


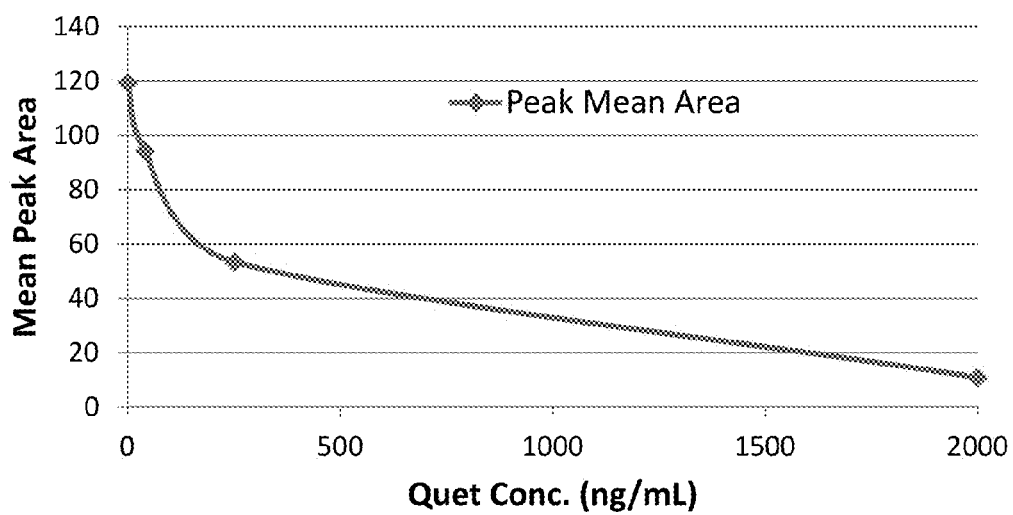
Fig. 9**QUET Peak Mean Area vs. Conc.
Clone 11**

Fig. 10

**RISP Peak Mean Area vs. Conc.
Clone 5-9**

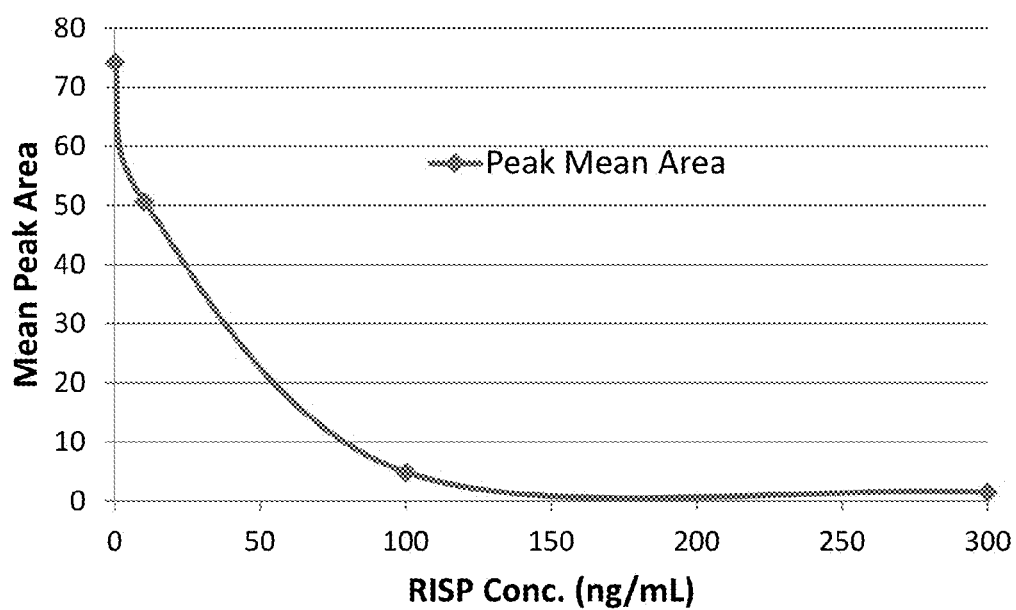


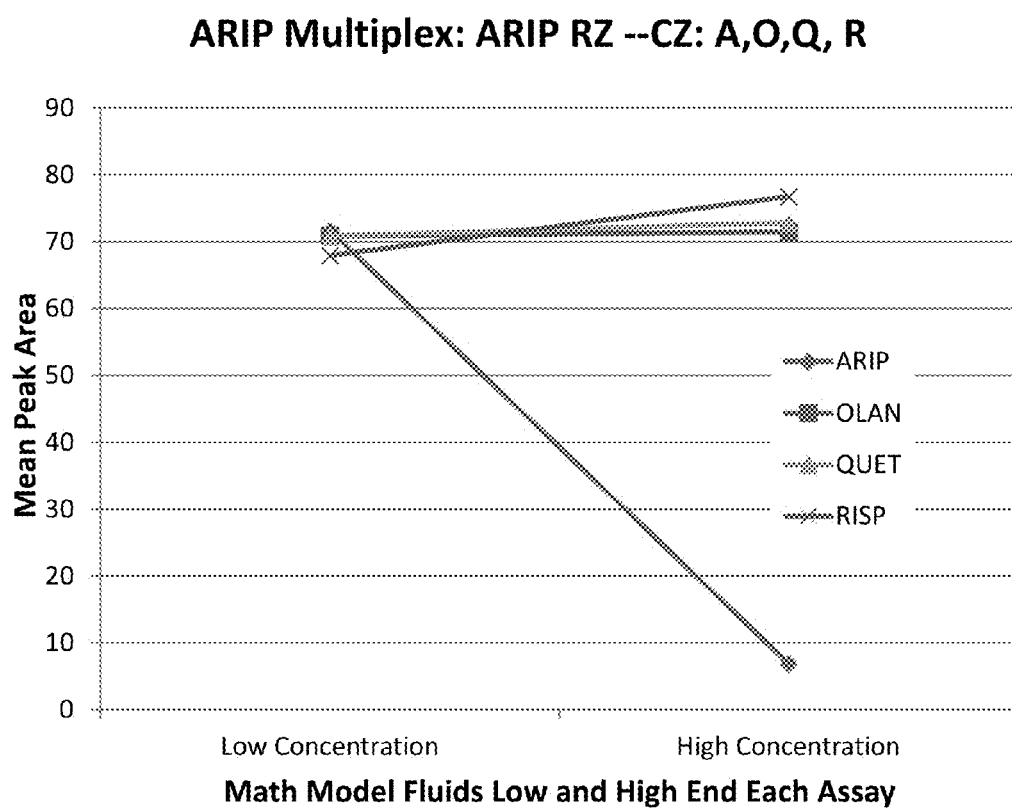
Fig. 11

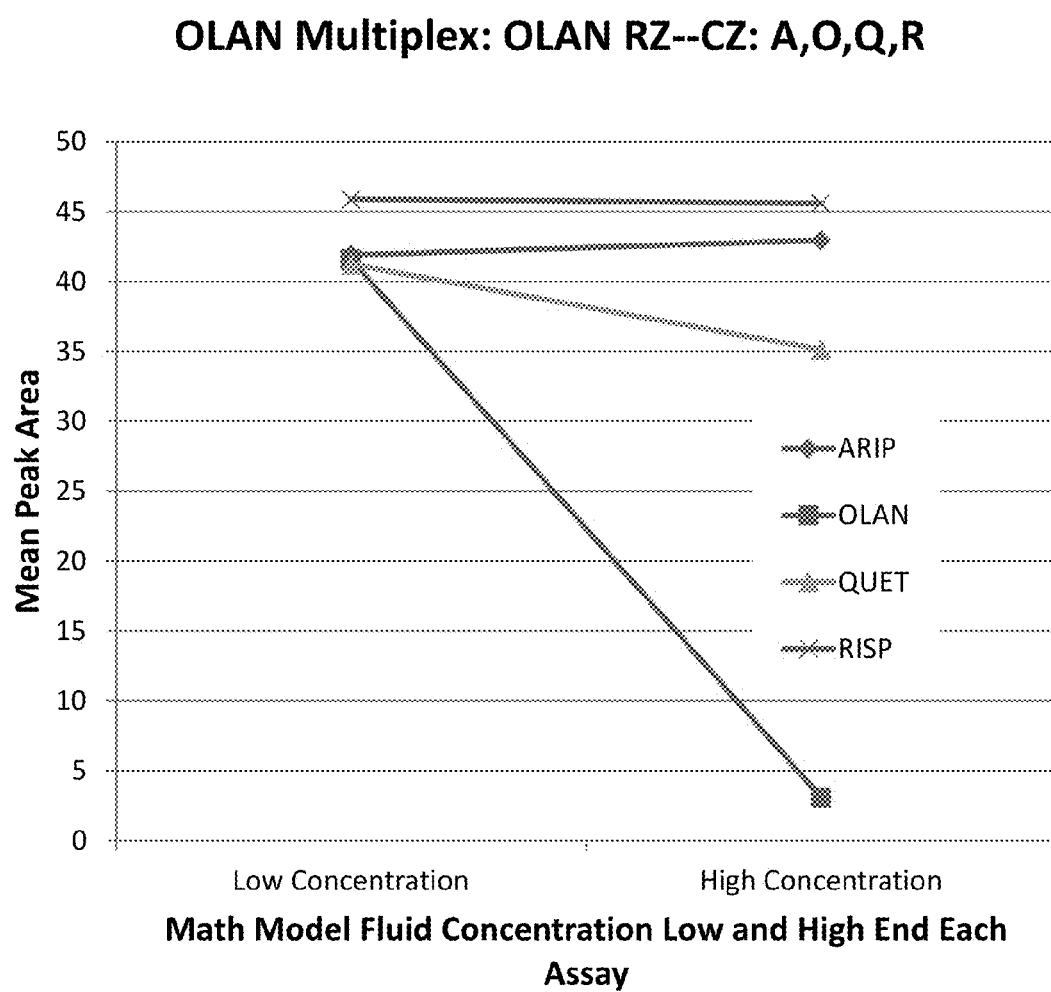
Fig. 12

Fig. 13

QUET Multiplex: QUET RZ--CZ: A,O,Q,R

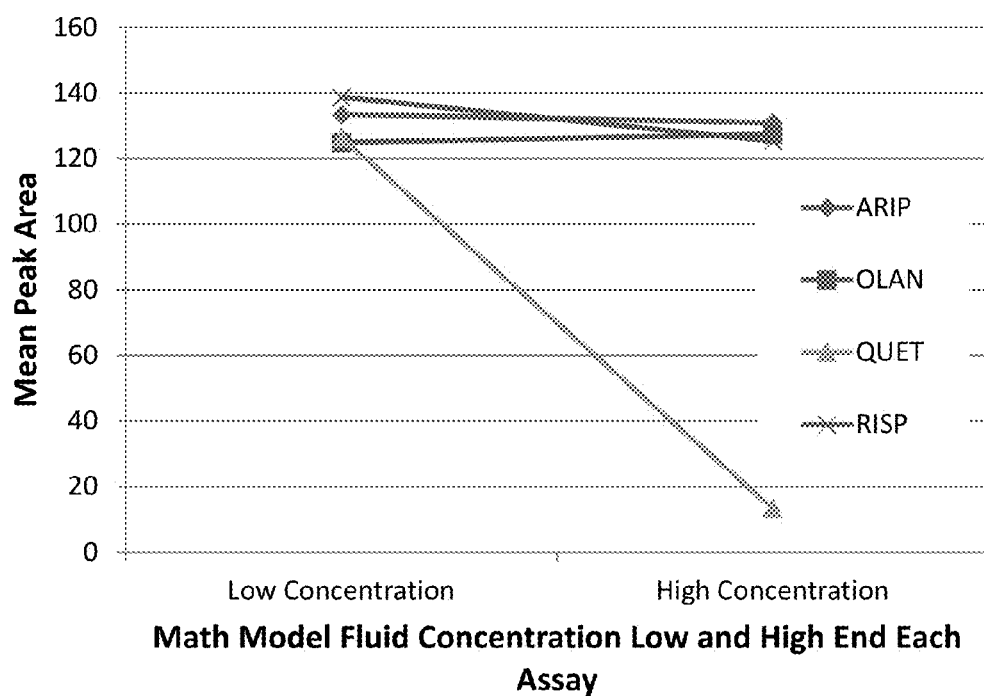


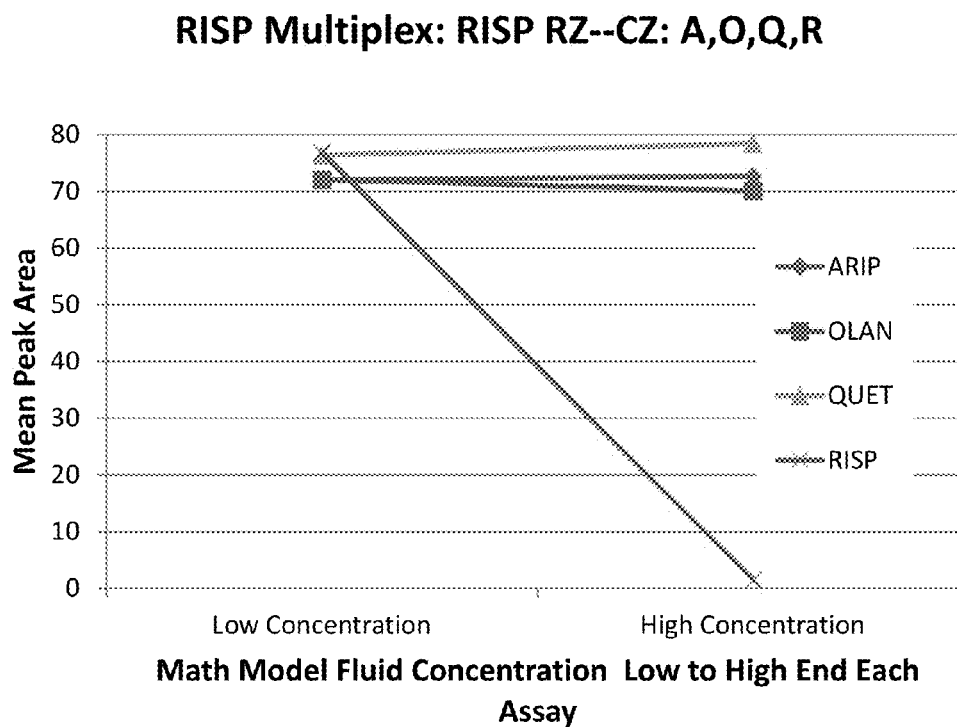
Fig. 14

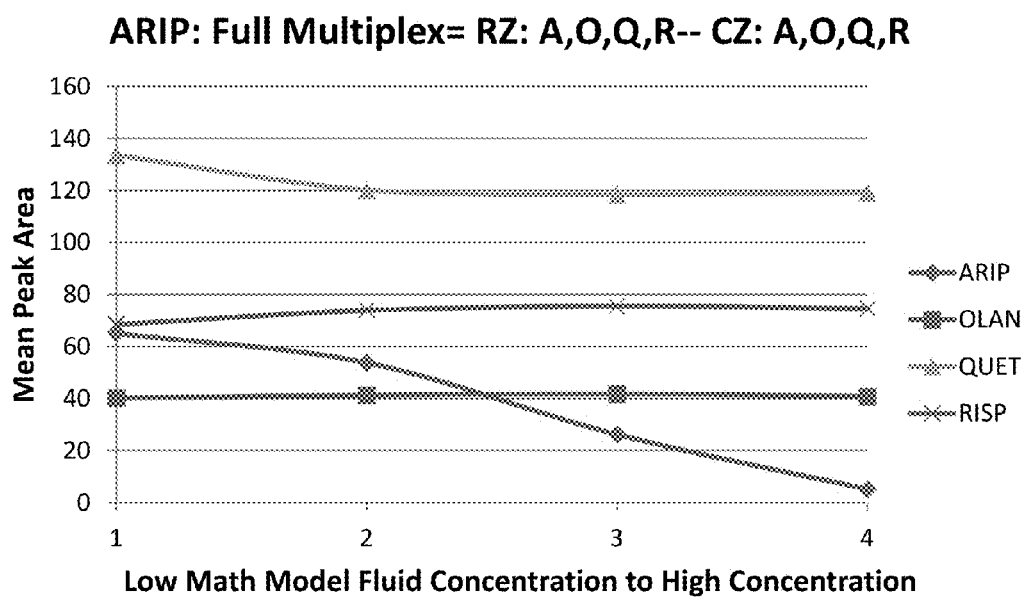
Fig. 15

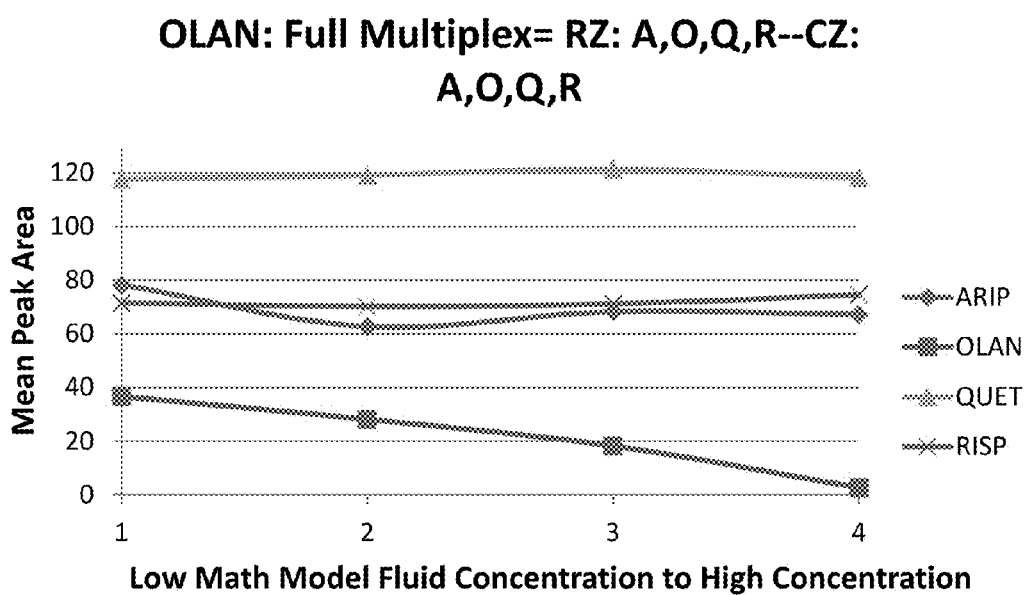
Fig. 16

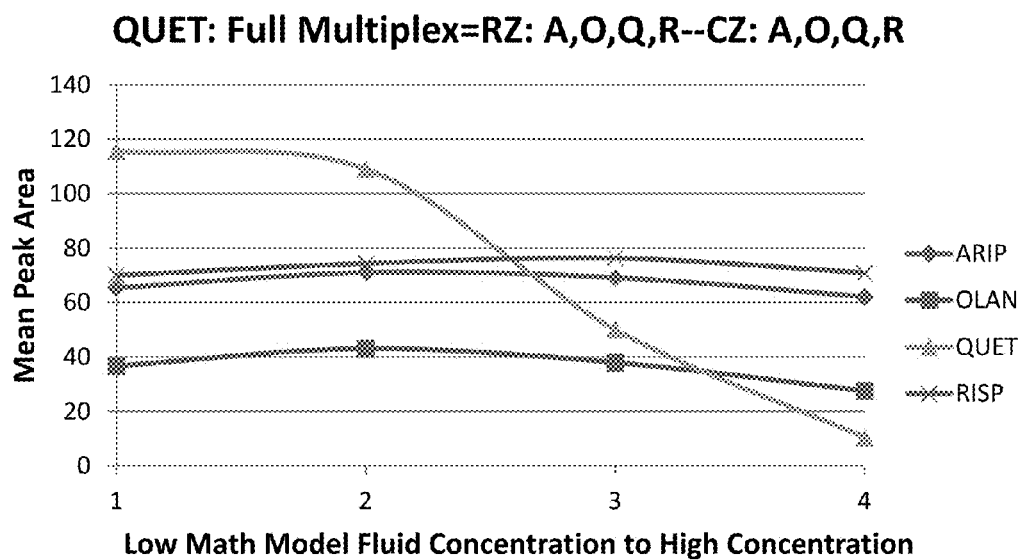
Fig. 17

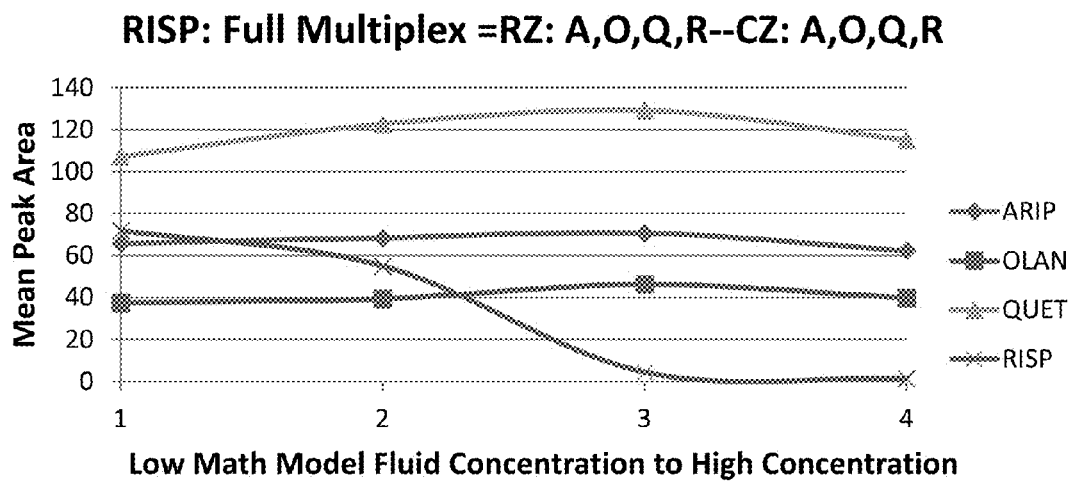
Fig. 18

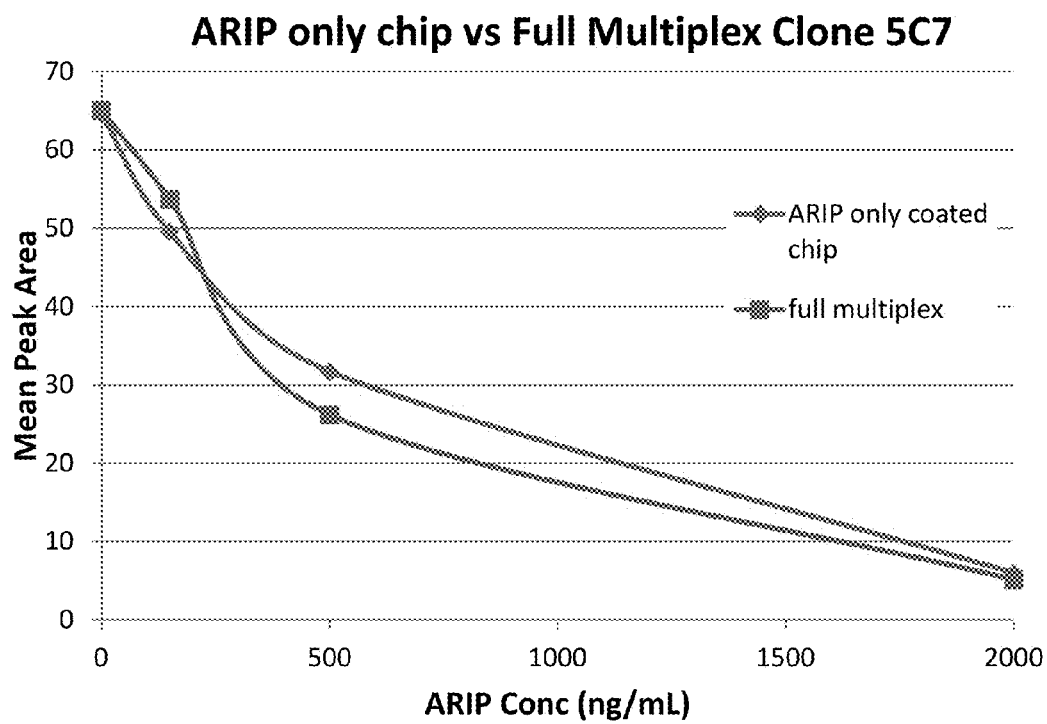
Fig. 19

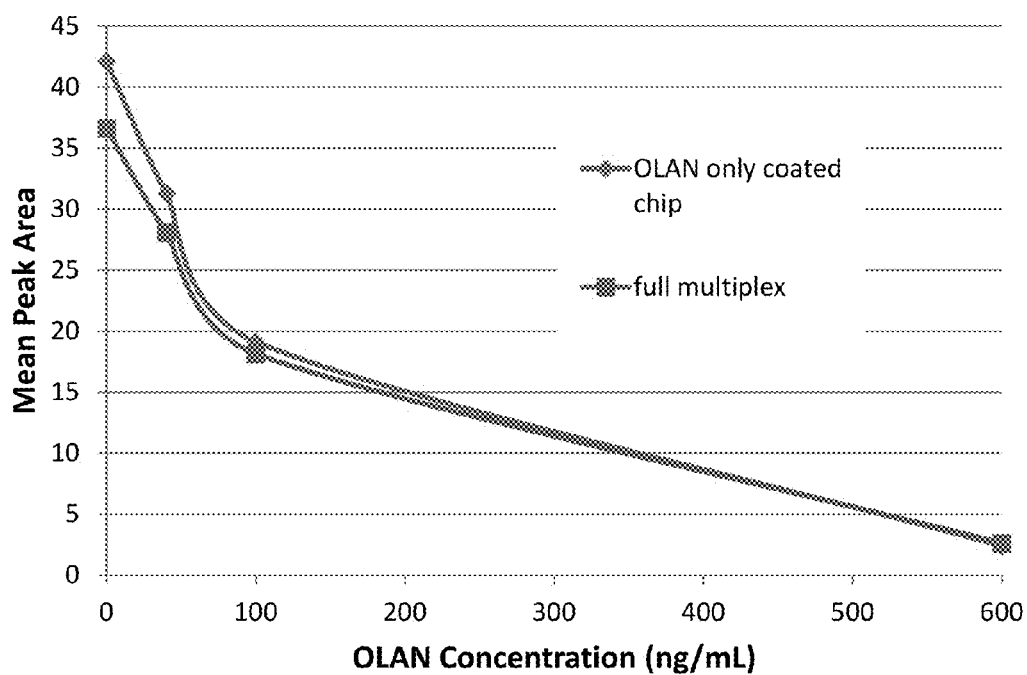
Fig. 20**OLAN only chip vs Full Multiplex 4G9-1**

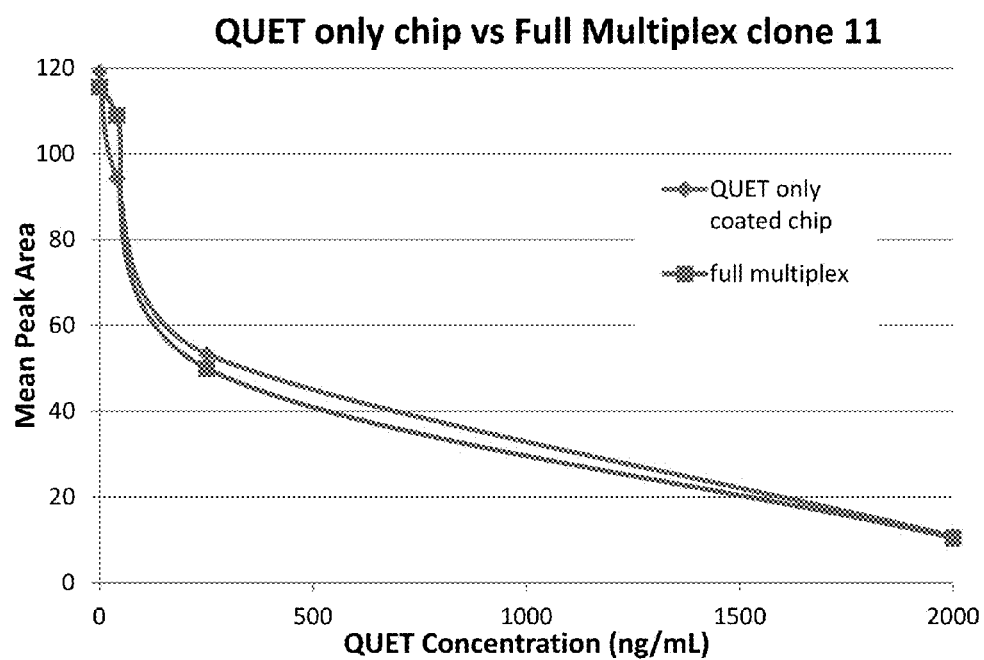
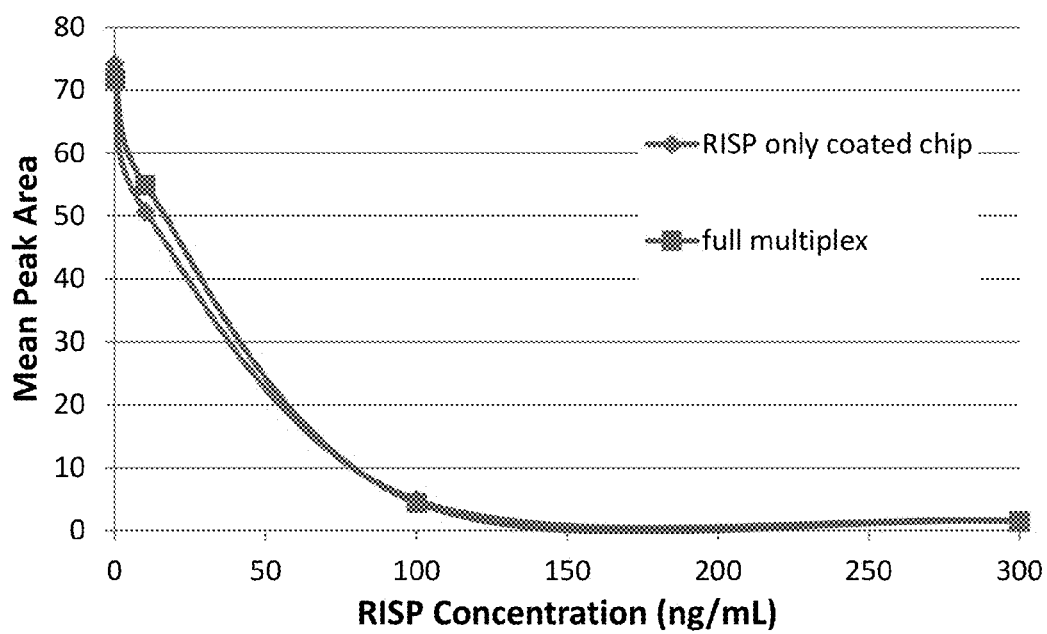
Fig. 21

Fig. 22**RISP only chip vs Full Multiplex Clone 5-9**

1

ANTIBODIES TO PALIPERIDONE AND USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/691,692, filed Aug. 21, 2012.

FIELD OF THE INVENTION

The present invention relates to the field of immunoassays, and in particular to antibodies that bind to paliperidone which can be used in immunoassays for detection of paliperidone.

BACKGROUND

Schizophrenia is a chronic and debilitating psychiatric disorder affecting approximately 0.45-1% of the world's population (van Os, J.; Kapur, S. "Schizophrenia" *Lancet* 2009, 374, 635-645). The principal goals of treatment are to achieve sustained remission from psychotic symptoms, reduce the risk and consequences of relapse, and improve patient functioning and overall quality of life. While many patients with schizophrenia are able to achieve symptom stability with the available antipsychotic medications, poor adherence to medication is a common reason for relapse with daily administered oral medications. Several studies (Abdel-Baki, A.; Ouellet-Plamondon, C.; Malla, A. "Pharmacotherapy Challenges in Patients with First-Episode Psychosis" *Journal of Affective Disorders* 2012, 138, S3-S14) investigating the outcomes of non-compliance have shown that patients with schizophrenia who do not take their medication as prescribed have higher rates of relapse, hospital admission and suicide as well as increased mortality. It is estimated that 40 to 75% of patients with schizophrenia have difficulty adhering to a daily oral treatment regimen (Lieberman, J. A.; Stroup, T. S.; McEvoy, J. P.; Swartz, M. S.; Rosenheck, R. A.; Perkins, D. O.; Keefe, R. S. E.; Davis, S. M.; Davis, C. E.; Lebowitz, B. D.; Severe, J.; Hsiao, J. K. "Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia" *New England Journal of Medicine* 2005, 353(12), 1209-1223).

Therapeutic drug monitoring (TDM) is the quantification of serum or plasma concentrations of drugs, including anti-psychotic drugs, for treatment monitoring and optimization. Such monitoring permits, for example, the identification of patients that are not adhering to their medication regimen, that are not achieving therapeutic doses, that are non-responsive at therapeutic doses, that have suboptimal tolerability, that have pharmacokinetic drug-drug interactions, or that have abnormal metabolism resulting in inappropriate plasma concentrations. Considerable individual variability exists in the patient's ability to absorb, distribute, metabolize, and excrete anti-psychotic drugs. Such differences can be caused by concurrent disease, age, concomitant medication or genetic peculiarities. Different drug formulations can also influence the metabolism of anti-psychotic drugs. TDM permits dose optimization for individual patients, improving therapeutic and functional outcomes. TDM further permits a prescribing clinician to ensure compliance with prescribed dosages and achievement of effective serum concentrations.

To date, methods for determining the levels of serum or plasma concentrations of anti-psychotic drugs involve the use of liquid chromatography (LC) with UV or mass spec-

2

trometry detection, and radioimmunoassays (see, for example, Woestenborghs et al., 1990 "On the selectivity of some recently developed RIA's" in *Methodological Surveys in Biochemistry and Analysis* 20:241-246. Analysis of Drugs and Metabolites, Including Anti-infective Agents; Heykants et al., 1994 "The Pharmacokinetics of Risperidone in Humans: A Summary", *J Clin Psychiatry* 55/5, suppl:13-17; Huang et al., 1993 "Pharmacokinetics of the novel anti-psychotic agent risperidone and the prolactin response in healthy subjects", *Clin Pharmacol Ther* 54:257-268). Radioimmunoassays detect one or both of risperidone and paliperidone. Salamone et al. in U.S. Pat. No. 8,088,594 disclose a competitive immunoassay for risperidone using antibodies that detect both risperidone and paliperidone but not pharmacologically inactive metabolites. The antibodies used in the competitive immunoassay are developed against a particular immunogen. ID Labs Inc. (London, Ontario, Canada) markets an ELISA for olanzapine, another anti-psychotic drug, which also utilizes a competitive format. The Instructions For Use indicate that the assay is designed for screening purposes and intended for forensic or research use, and is specifically not intended for therapeutic use. The Instructions recommend that all positive samples should be confirmed with gas chromatography/mass spectrometry (GC-MS), and indicate that the antibody used detects olanzapine and clozapine (see ID Labs Inc., "Instructions For Use Data Sheet IDEL-F083", Rev. Date Aug. 8, 2011). Some of these methods, namely HPLC and GC/MS, can be expensive and labor-intensive, and are generally only performed in large or specialty labs having the appropriate equipment.

A need exists for other methods for determining the levels of anti-psychotic drugs, particularly methods that can be performed in a prescribing clinician's office (where the treatment for an individual patient can be adjusted accordingly in a much more timely manner) and in other medical settings lacking LC or GC/MS equipment or requiring rapid test results.

SUMMARY OF THE INVENTION

The present invention is directed to an isolated antibody or a binding fragment thereof, which binds to paliperidone and which: (i) is an antibody selected from the group consisting of: a) an isolated antibody or a fragment thereof comprising a light chain variable region comprising the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:7; b) an isolated antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:8; c) an isolated antibody or a fragment thereof comprising a light chain variable region having the amino acid sequence of SEQ ID NO:3 and a heavy chain variable region having the amino acid sequence of SEQ ID NO:4; or d) an isolated antibody or a fragment thereof comprising a light chain variable region having the amino acid sequence of SEQ ID NO:7 and a heavy chain variable region having the amino acid sequence of SEQ ID NO:8; or (ii) competes for an epitope which is the same as an epitope bound by the antibody of (i).

The antibodies of the subject invention can be provided in assay kits and assay devices, with a presently preferred device being a lateral flow assay device which provides for point-of-care analysis.

The invention further provides a method of detecting paliperidone in a sample. The method comprises: (i) contacting a sample with an antibody according to the subject invention which is labeled with a detectable marker, wherein the labeled antibody and paliperidone present in the sample

form a labeled complex; and (ii) detecting the labeled complex so as to detect paliperidone in the sample.

Further provided is a competitive immunoassay method for detecting paliperidone in a sample. The method comprises: (i) contacting a sample with an antibody according to the subject invention, and with paliperidone or a competitive binding partner of paliperidone, wherein one of the antibody and the paliperidone or competitive binding partner thereof is labeled with a detectable marker, and wherein sample paliperidone competes with the paliperidone or competitive binding partner thereof for binding to the antibody; and (ii) detecting the label so as to detect sample paliperidone.

Further objects, features and advantages of the present invention will be apparent to those skilled in the art from detailed consideration of the preferred embodiments that follow.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1 and 2 show Competitive ELISA results generated with hybridoma 5-9;

FIG. 3 shows Competitive ELISA results generated with risperidone/paliperidone clone 2A5;

FIG. 4 shows the competitive immunoassay format used on a lateral flow assay device;

FIG. 5 shows a typical dose response curve generated with risperidone/paliperidone clone 5-9;

FIG. 6 shows the chip design of a lateral flow assay device according to the subject invention;

FIG. 7 shows a typical dose response curve for an aripiprazole positive control generated with antibody 5C7 and a labeled aripiprazole competitive binding partner;

FIG. 8 shows a typical dose response curve for an olanzapine positive control generated with antibody 4G9-1 and a labeled olanzapine competitive binding partner;

FIG. 9 shows a typical dose response curve for a quetiapine positive control generated with antibody 11 and a labeled quetiapine competitive binding partner;

FIG. 10 shows a typical dose response curve for a risperidone positive control generated with antibody 5-9 and a labeled risperidone competitive binding partner;

FIG. 11 shows a typical dose response curve for a sample containing aripiprazole generated with aripiprazole antibody 5C7 in the presence of labeled aripiprazole competitive binding partner, with no dose response curve for olanzapine, quetiapine, or risperidone in the presence of a labeled competitive binding partner for each;

FIG. 12 shows a typical dose response curve for a sample containing olanzapine generated with olanzapine antibody 4G9-1 in the presence of a labeled olanzapine competitive binding partner, with no dose response curve for aripiprazole, quetiapine, or risperidone in the presence of a labeled competitive binding partner for each;

FIG. 13 shows a typical dose response curve for a sample containing quetiapine generated with quetiapine antibody 11 in the presence of a labeled quetiapine competitive binding partner, with no dose response curve for aripiprazole, olanzapine, or risperidone in the presence of a labeled competitive binding partner for each;

FIG. 14 shows a typical dose response curve for a sample containing risperidone generated with risperidone antibody 5-9 in the presence of a labeled risperidone competitive binding partner, with no dose response curve for aripiprazole, olanzapine, or quetiapine in the presence of a labeled competitive binding partner for each;

FIG. 15 shows a typical dose response curve for a sample containing aripiprazole generated with aripiprazole antibody

5C7 in the presence of a labeled aripiprazole competitive binding partner, with no dose response curve for olanzapine, quetiapine, or risperidone in the presence of antibody and labeled competitive binding partner for each;

FIG. 16 shows a typical dose response curve for a sample containing olanzapine generated with olanzapine antibody 4G9-1 in the presence of a labeled olanzapine competitive binding partner, with no dose response curve for aripiprazole, quetiapine, or risperidone in the presence of antibody and labeled competitive binding partner for each;

FIG. 17 shows a typical dose response curve for a sample containing quetiapine generated with quetiapine antibody 11 in the presence of labeled quetiapine competitive binding partner, with no dose response curve for aripiprazole, olanzapine, or risperidone in the presence of antibody and labeled competitive binding partner for each;

FIG. 18 shows a typical dose response curve for a sample containing risperidone generated with risperidone antibody 5-9 in the presence of a labeled risperidone competitive binding partner, with no dose response curve for aripiprazole, olanzapine, or quetiapine in the presence of antibody and labeled competitive binding partner for each;

FIG. 19 shows a comparison of the aripiprazole dose response curve generated as a positive control to the aripiprazole dose response curve generated in the multiplex format;

FIG. 20 shows a comparison of the olanzapine dose response curve generated as a positive control to the olanzapine dose response curve generated in the multiplex format;

FIG. 21 shows a comparison of the quetiapine dose response curve generated as a positive control to the quetiapine dose response curve generated in the multiplex format; and

FIG. 22 shows a comparison of the risperidone dose response curve generated as a positive control to the risperidone dose response curve generated in the multiplex format.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The following terms are used to describe the sequence relationships between two or more polynucleotide or amino acid sequences: "reference sequence", "comparison window", "sequence identity", "percentage of sequence identity", "substantial identity", "similarity", and "homologous". A "reference sequence" is a defined sequence used as a basis for a sequence comparison; a reference sequence may be a subset of a larger sequence, for example, a segment of a full length cDNA or gene sequence given in a sequence listing or may comprise a complete cDNA or gene sequence; a reference sequence may comprise a segment of a complete amino acid sequence encoding a protein as given in a sequence listing or may comprise a complete amino acid sequence encoding a protein. Generally, a reference sequence is at least 18 nucleotides or 6 amino acids in length, frequently at least 24 nucleotides or 8 amino acids in length, and often at least 48 nucleotides or 16 amino acids in length. Since two polynucleotide or amino acid sequences may each (1) comprise a sequence (i.e., a portion of the complete nucleotide or amino acid sequence) that is similar between the two molecules, and (2) may further comprise a sequence that is divergent between the two polynucleotide or amino acid sequences, sequence comparisons between two (or more) molecules are typically performed by comparing sequences of the two molecules over a "comparison window" to identify and compare local regions of sequence

similarity. A “comparison window”, as used herein, refers to a conceptual segment of at least 18 contiguous nucleotide positions or 6 amino acids wherein the polynucleotide sequence or amino acid sequence may be compared to a reference sequence of at least 18 contiguous nucleotides or 6 amino acids and wherein the portion of the polynucleotide sequence or amino acid sequence in the comparison window may comprise additions, deletions, substitutions, and the like (i.e., gaps) of 20 percent or less as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Optimal alignment of sequences for aligning a comparison window may be conducted by the local homology algorithm of Smith and Waterman, *Adv. Appl. Math.* 2:482 (1981), by the homology alignment algorithm of Needleman and Wunsch, *J. Mol. Biol.* 48:443 (1970), by the search for similarity method of Pearson and Lipman, *Proc. Natl. Acad. Sci. USA* 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package Release 7.0 (Genetics Computer Group, 575 Science Dr., Madison, Wis.), Geneworks or MacVector software packages), or by inspection, and the best alignment (i.e., resulting in the highest percentage of identity over the comparison window) generated by the various methods is selected.

The term “sequence identity” means that two polynucleotide or amino acid sequences are identical (i.e., on a nucleotide-by-nucleotide or amino acid residue-by-residue basis) over the comparison window. The term “percentage of sequence identity” is calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (e.g., A, T, C, G, or U) or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the comparison window (i.e., the window size), and multiplying the result by 100 to yield the percentage of sequence identity. The term “substantial identity” as used herein denotes a characteristic of a polynucleotide or amino acid sequence, wherein the polynucleotide or amino acid sequence comprises a sequence that has at least 85 percent sequence identity, preferably at least 90 to 95 percent sequence identity, more usually at least 99 percent sequence identity as compared to a reference sequence over a comparison window of at least 18 nucleotide (6 amino acid) positions, frequently over a window of at least 24-48 nucleotide (8-16 amino acid) positions, wherein the percentage of sequence identity is calculated by comparing the reference sequence to the sequence which may include deletions or additions which total 20 percent or less of the reference sequence over the comparison window. The reference sequence may be a subset of a larger sequence. The term “similarity”, when used to describe a polypeptide, is determined by comparing the amino acid sequence and the conserved amino acid substitutions of one polypeptide to the sequence of a second polypeptide. The term “homologous”, when used to describe a polynucleotide, indicates that two polynucleotides, or designated sequences thereof, when optimally aligned and compared, are identical, with appropriate nucleotide insertions or deletions, in at least 70% of the nucleotides, usually from about 75% to 99%, and more preferably at least about 98% to 99% of the nucleotides.

A “label,” “detector molecule,” “reporter” or “detectable marker” as used herein is any molecule which produces, or can be induced to produce, a detectable signal. The label can be conjugated to an analyte, immunogen, antibody, or to

another molecule such as a receptor or a molecule that can bind to a receptor such as a ligand, particularly a hapten or antibody. A label can be attached directly or indirectly by means of a linking or bridging moiety. Non-limiting examples of labels include radioactive isotopes (e.g., ¹²⁵I), enzymes (e.g. β -galactosidase, peroxidase), enzyme fragments, enzyme substrates, enzyme inhibitors, coenzymes, catalysts, fluorophores (e.g., rhodamine, fluorescein isothiocyanate or FITC, or Dylight 649), dyes, chemiluminescers and luminescers (e.g., dioxetanes, luciferin), or sensitizers.

The invention provides an isolated antibody which binds to paliperidone. The invention further provides an assay kit and an assay device comprising the antibody. Further provided is a method of detecting paliperidone in a sample, including a competitive immunoassay method.

In one embodiment, the present invention is directed to an isolated antibody or a binding fragment thereof, which binds to paliperidone and which: (i) is an antibody selected from the group consisting of: a) an isolated antibody or a fragment thereof comprising a light chain variable region comprising the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:7; b) an isolated antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:8; c) an isolated antibody or a fragment thereof comprising a light chain variable region having the amino acid sequence of SEQ ID NO:3 and a heavy chain variable region having the amino acid sequence of SEQ ID NO:4; or d) an isolated antibody or a fragment thereof comprising a light chain variable region having the amino acid sequence of SEQ ID NO:7 and a heavy chain variable region having the amino acid sequence of SEQ ID NO:8; or (ii) competes for an epitope bound by the antibody of (i).

In a further embodiment, the present invention is directed to an isolated antibody or a binding fragment thereof, which binds to paliperidone and which comprises a light chain variable region comprising an amino acid sequence having at least 80% sequence identity with SEQ ID NO:3 or SEQ ID NO:7.

In a further embodiment, the present invention is directed to an isolated antibody or a binding fragment thereof, which binds to paliperidone and which comprises a heavy chain variable region comprising an amino acid sequence having at least 80% sequence identity with SEQ ID NO:4 or SEQ ID NO:8.

Presently preferred embodiments of the antibody of the subject invention are: an antibody which comprises a light chain variable region having the amino acid sequence SEQ ID NO:3 and a heavy chain variable region having the amino acid sequence SEQ ID NO:4; and an antibody which comprises a light chain variable region having the amino acid sequence SEQ ID NO:7 and a heavy chain variable region having the amino acid sequence SEQ ID NO:8.

Additional presently preferred embodiments of the antibody of the subject invention are: 1) an antibody which comprises a light chain CDR1 sequence comprising amino acid residues 44 to 60 of SEQ ID NO:3, a light chain CDR2 sequence comprising amino acid residues 76 to 82 of SEQ ID NO:3, a light chain CDR3 sequence comprising amino acid residues 115 to 123 of SEQ ID NO:3, a heavy chain CDR1 sequence comprising amino acid residues 45 to 54 of SEQ ID NO:4, a heavy chain CDR2 sequence comprising amino acid residues 69 to 85 of SEQ ID NO:4, and a heavy chain CDR3 sequence comprising amino acid residues 118 to 122 of SEQ ID NO:4; and 2) an antibody which comprises a light chain CDR1 sequence comprising amino acid residues 44 to 60 of SEQ ID NO:7, a light chain CDR2 sequence

comprising amino acid residues 76 to 82 of SEQ ID NO:7, a light chain CDR3 sequence comprising amino acid residues 115 to 123 of SEQ ID NO:7, a heavy chain CDR1 sequence comprising amino acid residues 45 to 54 of SEQ ID NO:8, a heavy chain CDR2 sequence comprising amino acid residues 69 to 85 of SEQ ID NO:8, and a heavy chain CDR3 sequence comprising amino acid residues 118 to 122 of SEQ ID NO:8.

Further details of the antibodies of the subject invention are provided in the section below entitled "Antibodies".

The subject invention further provides an assay kit comprising the antibody, as well as an assay device comprising the antibody. Preferably, the assay device is a lateral flow assay device. Further details of the assay kits and assay devices are provided below in the section entitled "Assay Kits and Devices".

The invention further provides a method of detecting paliperidone in a sample. The method comprises: (i) contacting a sample with an antibody according to the subject invention which is labeled with a detectable marker, wherein the labeled antibody and paliperidone present in the sample form a labeled complex; and (ii) detecting the labeled complex so as to detect paliperidone in the sample. Further details of the method of detecting paliperidone in accordance with the subject invention are provided in the section below entitled "Immunoassays".

Further provided is a competitive immunoassay method for detecting paliperidone in a sample. The method comprises: (i) contacting a sample with an antibody according to the subject invention, and with paliperidone or a competitive binding partner of paliperidone, wherein one of the antibody and the paliperidone or competitive binding partner thereof is labeled with a detectable marker, and wherein sample paliperidone competes with the paliperidone or competitive binding partner thereof for binding to the antibody; and (ii) detecting the label so as to detect sample paliperidone. Further details of the competitive immunoassay method of detecting paliperidone in accordance with the subject invention are provided in the section below entitled "Immunoassays".

In a preferred embodiment of the subject invention, the detection of paliperidone is accompanied by the detection of one or more analytes in addition to paliperidone. Preferably the one or more analytes are anti-psychotic drugs other than paliperidone, and more preferably the anti-psychotic drugs other than paliperidone are selected from the group consisting of: aripiprazole, risperidone, quetiapine, olanzapine, and metabolites thereof.

As discussed above, the antibodies of the subject invention can be used in assays to detect the presence and/or amount of the anti-psychotic drug in patient samples. Such detection permits therapeutic drug monitoring enabling all of the benefits thereof. Detection of levels of anti-psychotic drugs may be useful for many purposes, each of which represents another embodiment of the subject invention, including: determination of patient adherence or compliance with prescribed therapy; use as a decision tool to determine whether a patient should be converted from an oral anti-psychotic regimen to a long-acting injectable anti-psychotic regimen; use as a decision tool to determine if the dose level or dosing interval of oral or injectable anti-psychotics should be increased or decreased to ensure attainment or maintenance of efficacious or safe drug levels; use as an aid in the initiation of anti-psychotic drug therapy by providing evidence of the attainment of minimum pK levels; use to determine bioequivalence of anti-psychotic drug in multiple formulations or from multiple sources; use to assess the

impact of polypharmacy and potential drug-drug interactions; and use as an indication that a patient should be excluded from or included in a clinical trial and as an aid in the subsequent monitoring of adherence to clinical trial medication requirements.

Antibodies

The present invention provides an isolated antibody which binds to paliperidone. The term "antibody" refers to a specific protein capable of binding an antigen or portion thereof (in accordance with this invention, capable of binding to an anti-psychotic drug or metabolite thereof). An antibody is produced in response to an immunogen which may have been introduced into a host, e.g., an animal or a human, by injection. The generic term "antibody" includes polyclonal antibodies, monoclonal antibodies, and antibody fragments.

"Antibody" or "antigen-binding antibody fragment" refers to an intact antibody, or a fragment thereof, that competes with the intact antibody for binding. Generally speaking, an antibody or antigen-binding antibody fragment, is said to specifically bind an antigen when the dissociation constant is less than or equal to 1 μ M, preferably less than or equal to 100 nM and most preferably less than or equal to 10 nM. Binding can be measured by methods known to those skilled in the art, an example being the use of a BIAcore™ instrument.

Antibodies are made up of two heavy chains and two light chains. Each heavy chain has one variable domain or region (V_H) followed by a constant domain or region (C_H1), a hinge region, and two more constant domains or regions (C_H2 and C_H3). Each light chain has one variable domain or region (V_L) and one constant domain or region (C_L). The variable domains or regions of the heavy and light chains form the paratope of the antibody (a structure analogous to a lock), which is specific for a particular epitope (similarly analogous to a key), allowing the paratope and the epitope to bind together with precision. Within the variable domain, variable loops of β -strands, three each on the light and heavy chains, are responsible for binding to the antigen. These loops are referred to as the complementarity determining regions (CDRs, namely CDR1, CDR2, and CDR3).

Antibody fragments comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Binding fragments include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; minibodies; linear antibodies; single-chain antibody molecules (e.g., scFV); and multispecific antibodies formed from antibody fragments. An antibody other than a "bispecific" or "bifunctional" antibody is understood to have each of its binding sites identical.

As used herein, "epitope" includes any protein determinant capable of specific binding to an immunoglobulin or T-cell receptor. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. Two antibodies are said to "bind the same epitope" ("compete") if one antibody is shown to compete with the second antibody in a competitive binding assay, by any of the methods well known to those skilled in the art (such as the BIAcore™ method referred to above). In reference to a hapten (such as paliperidone or other anti-psychotic drug), an antibody can be generated against the non-antigenic hapten molecule by conjugating the hapten to an immunogenic carrier. An antibody is then generated which recognizes an "epitope" defined by the hapten.

"Isolated" when used in the context of an antibody means altered "by the hand of man" from any natural state; i.e.,

that, if it occurs in nature, it has been changed or removed from its original environment, or both. For example, a naturally occurring antibody naturally present in a living animal in its natural state is not "isolated", but the same antibody separated from the coexisting materials of its natural state is "isolated", as the term is employed herein. Antibodies may occur in a composition, such as an immunoassay reagent, which are not naturally occurring compositions, and therein remain isolated antibodies within the meaning of that term as it is employed herein.

"Cross-reactivity" refers to the reaction of an antibody with an antigen that was not used to induce that antibody.

Preferably, the antibody of the subject invention will bind to the drug and any desired pharmacologically active metabolites. By altering the location of the attachment of an immunogenic carrier in a drug conjugate, selectivity and cross-reactivity with metabolites and/or related drugs can be engineered into the antibodies. For paliperidone (9-hydroxy-risperidone), cross-reactivity with risperidone or other risperidone metabolites such as 7-hydroxyrisperidone and N-dealkylrisperidone may or may not be desirable. An antibody that cross-reacts with risperidone and paliperidone may be desirable, which does not react with 7-hydroxyrisperidone or N-dealkylrisperidone, thus detecting risperidone and its major pharmacologically active metabolite paliperidone. Alternatively, it may be desirable to detect the pharmacologically active metabolites, risperidone and paliperidone, separately, while still not detecting the inactive metabolites, 7-hydroxyrisperidone and N-dealkylrisperidone. Antibodies may be generated that detect multiple ones of these drugs and/or metabolites, or antibodies may be generated that detect each separately (thus defining the antibody "specific binding" properties). An antibody specifically binds one or more compounds when its binding of the one or more compounds is equimolar or substantially equimolar.

The antibodies herein are described by the nucleotide and amino acid sequences of their variable domains. Each was generated by inoculating a host with a conjugate comprising an anti-psychotic drug conjugated to an immunogenic carrier. Having now provided the nucleotide and amino acid sequences thereof, the antibodies can be produced by the recombinant methods such as are described in U.S. Pat. No. 4,166,452.

Antibody fragments which contain specific binding sites for the anti-psychotic drug may also be generated. Such fragments include, but are not limited to, the $F(ab')_2$ fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the $F(ab')_2$ fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity (Huse et al., *Science* 256:1270-1281 (1989)). Fab, Fv and ScFv antibody fragments can all be expressed in and secreted from *Escherichia coli*, allowing for the production of large amounts of these fragments. Alternatively, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form $F(ab')_2$ fragments (Carter et al., *BioTechnology* 10:163-167 (1992)). Other techniques for the production of antibody fragments are known to those skilled in the art. Single chain Fv fragments (scFv) are also envisioned (see U.S. Pat. Nos. 5,761,894 and 5,587,458). Fv and sFv fragments are the only species with intact combining sites that are devoid of constant regions; thus, they are likely to show reduced non-specific binding. The antibody fragment may also be a "linear antibody" e.g., as described in U.S.

Pat. No. 5,642,870, for example. Such linear antibody fragments may be monospecific or bispecific.

Assay Kits and Devices

An assay kit (also referred to as a reagent kit) can also be provided comprising an antibody as described above. A representative reagent kit may comprise an antibody that binds to the anti-psychotic drug, paliperidone, a complex comprising an analog of an anti-psychotic drug or a derivative thereof coupled to a labeling moiety, and may optionally also comprise one or more calibrators comprising a known amount of an anti-psychotic drug or a related standard.

The phrase "assay kit" refers to an assembly of materials and reagents that is used in performing an assay. The reagents can be provided in packaged combination in the same or in separate containers, depending on their cross-reactivities and stabilities, and in liquid or in lyophilized form. The amounts and proportions of reagents provided in the kit can be selected so as to provide optimum results for a particular application. An assay kit embodying features of the present invention comprises antibodies which bind paliperidone. The kit may further comprise competitive binding partners of paliperidone and calibration and control materials.

The phrase "calibration and control material" refers to any standard or reference material containing a known amount of an analyte. A sample suspected of containing an analyte and the corresponding calibration material are assayed under similar conditions. The concentration of analyte is calculated by comparing the results obtained for the unknown specimen with the results obtained for the standard. This is commonly done by constructing a calibration curve.

Antibodies embodying features of the present invention can be included in a kit, container, pack, or dispenser together with instructions for their utilization. When the antibodies are supplied in a kit, the different components of the immunoassay may be packaged in separate containers and admixed prior to use. Such packaging of the components separately may permit long-term storage without substantially diminishing the functioning of the active components. Furthermore, reagents can be packaged under inert environments, e.g., under a positive pressure of nitrogen gas, argon gas, or the like, which is especially preferred for reagents that are sensitive to air and/or moisture.

Reagents included in kits embodying features of the present invention can be supplied in all manner of containers such that the activities of the different components are substantially preserved while the components themselves are not substantially adsorbed or altered by the materials of the container. Suitable containers include, but are not limited to, ampules, bottles, test tubes, vials, flasks, syringes, envelopes, e.g., foil-lined, and the like. The containers may be comprised of any suitable material including, but not limited to, glass, organic polymers, e.g., polycarbonate, polystyrene, polyethylene, etc., ceramic, metal, e.g., aluminum, metal alloys, e.g., steel, cork, and the like. In addition, the containers may comprise one or more sterile access ports, e.g., for access via a needle, such as may be provided by a septum. Preferred materials for septa include rubber and polytetrafluoroethylene of the type sold under the trade name TEFLON by DuPont (Wilmington, Del.). In addition, the containers may comprise two or more compartments separated by partitions or membranes that can be removed to allow mixing of the components.

Reagent kits embodying features of the present invention may also be supplied with instructional materials. Instructions may be printed, e.g., on paper and/or supplied in an electronically-readable medium. Alternatively, instructions

may be provided by directing a user to an internet website, e.g., specified by the manufacturer or distributor of the kit and/or via electronic mail.

The antibody may also be provided as part of an assay device. Such assay devices include lateral flow assay devices. A common type of disposable lateral flow assay device includes a zone or area for receiving the liquid sample, a conjugate zone, and a reaction zone. These assay devices are commonly known as lateral flow test strips. They employ a porous material, e.g., nitrocellulose, defining a path for fluid flow capable of supporting capillary flow. Examples include those shown in U.S. Pat. Nos. 5,559,041, 5,714,389, 5,120,643, and 6,228,660 all of which are incorporated herein by reference in their entireties.

Another type of assay device is a non-porous assay device having projections to induce capillary flow. Examples of such assay devices include the open lateral flow device as disclosed in PCT International Publication Nos. WO 2003/103835, WO 2005/089082, WO 2005/118139, and WO 2006/137785, all of which are incorporated herein by reference in their entireties.

In a non-porous assay device, the assay device generally has at least one sample addition zone, at least one conjugate zone, at least one reaction zone, and at least one wicking zone. The zones form a flow path by which sample flows from the sample addition zone to the wicking zone. Also included are capture elements, such as antibodies, in the reaction zone, capable of binding to the analyte, optionally deposited on the device (such as by coating); and a labeled conjugate material also capable of participating in reactions that will enable determination of the concentration of the analyte, deposited on the device in the conjugate zone, wherein the labeled conjugate material carries a label for detection in the reaction zone. The conjugate material is dissolved as the sample flows through the conjugate zone forming a conjugate plume of dissolved labeled conjugate material and sample that flows downstream to the reaction zone. As the conjugate plume flows into the reaction zone, the conjugated material will be captured by the capture elements such as via a complex of conjugated material and analyte (as in a "sandwich" assay) or directly (as in a "competitive" assay). Unbound dissolved conjugate material will be swept past the reaction zone into the at least one wicking zone. Such devices can include projections or micropillars in the flow path.

An instrument such as that disclosed in US Patent Publication Nos. US20060289787A1 and US 20070231883A1, and U.S. Pat. Nos. 7,416,700 and 6,139,800, all of which are incorporated herein by reference in their entireties, is able to detect the bound conjugated material in the reaction zone. Common labels include fluorescent dyes that can be detected by instruments which excite the fluorescent dyes and incorporate a detector capable of detecting the fluorescent dyes. Immunoassays

The antibodies thus produced can be used in immunoassays to recognize/bind to the anti-psychotic drug, thereby detecting the presence and/or amount of the drug in a patient sample. Preferably, the assay format is a competitive immunoassay format. Such an assay format and other assays are described, among other places, in Hampton et al. (*Serological Methods, A Laboratory Manual*, APS Press, St. Paul, Minn. 1990) and Maddox et al. (*J. Exp. Med.* 158:12111, 1983).

The term "analyte" refers to any substance or group of substances, the presence or amount of which is to be determined. Representative anti-psychotic drug analytes

include, but are not limited to, risperidone, paliperidone, olanzapine, aripiprazole, and quetiapine.

The term "competitive binding partner" refers to a substance or group of substances, such as may be employed in a competitive immunoassay, which behave similarly to an analyte with respect to binding affinity to an antibody. Representative competitive binding partners include, but are not limited to, anti-psychotic drug derivatives and the like.

The term "detecting" when used with an analyte refers to any quantitative, semi-quantitative, or qualitative method as well as to all other methods for determining an analyte in general, and an anti-psychotic drug in particular. For example, a method that merely detects the presence or absence of an anti-psychotic drug in a sample lies within the scope of the present invention, as do methods that provide data as to the amount or concentration of the anti-psychotic drug in the sample. The terms "detecting", "determining", "identifying", and the like are used synonymously herein, and all lie within the scope of the present invention.

A preferred embodiment of the subject invention is a competitive immunoassay wherein antibodies which bind the anti-psychotic drug, or the drug or competitive binding partner thereof, are attached to a solid support (such as the reaction zone in a lateral flow assay device) and labeled drug or competitive binding partner thereof, or labeled antibody, respectively, and a sample derived from the host are passed over the solid support and the amount of label detected attached to the solid support can be correlated to a quantity of drug in the sample.

Any sample that is suspected of containing an analyte, e.g., an anti-psychotic drug, can be analyzed in accordance with the methods of the presently preferred embodiments. The sample can be pretreated if desired and can be prepared in any convenient medium that does not interfere with the assay. Preferably, the sample comprises an aqueous medium such as a body fluid from a host, most preferably plasma or serum.

It is to be understood that all manner of immunoassays employing antibodies are contemplated for use in accordance with the presently preferred embodiments, including assays in which antibodies are bound to solid phases and assays in which antibodies are in liquid media. Methods of immunoassays that can be used to detect analytes using antibodies embodying features of the present invention include, but are not limited to, competitive (reagent limited) assays wherein labeled analyte (analyte analog) and analyte in a sample compete for antibodies and single-site immunometric assays wherein the antibody is labeled; and the like.

All examples were carried out using standard techniques, which are well known and routine to those of skill in the art, except where otherwise described in detail. Routine molecular biology techniques of the following examples can be carried out as described in standard laboratory manuals, such as Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989).

Copending applications entitled "Haptens of Aripiprazole" (U.S. Provisional Patent Application No. 61/691,450, filed Aug. 21, 2012, and US 20140163206, filed Aug. 20, 2013, "Haptens of Olanzapine" (U.S. Provisional Patent Application No. 61/691,454, filed Aug. 21, 2012, and U.S. 20140213766, filed Aug. 20, 2013, "Haptens of Paliperidone" (U.S. Provisional Patent Application No. 61/691,459, filed Aug. 21, 2012, and US 20140213767, filed Aug. 20, 2013, "Haptens of Quetiapine" (U.S. Provisional Patent Application No. 61/691,462, filed Aug. 21, 2012, and US

13

20140221616, filed Aug. 20, 2013, "Haptens of Risperidone and Paliperidone" (U.S. Provisional Patent Application No. 61/691,469, filed Aug. 21, 2012, and US 20140155585, Aug. 20, 2013, "Antibodies to Aripiprazole Haptens and Use Thereof" (US Provisional Patent Application No. 61/691,544, filed Aug. 21, 2012, and US 20140057299, filed Aug. 20, 2013, "Antibodies to Olanzapine Haptens and Use Thereof" (U.S. Provisional Patent Application No. 61/691,572, filed Aug. 21, 2012, US 20140057303, filed Aug. 20, 2013, "Antibodies to Paliperidone Haptens and Use Thereof" (US Provisional Patent Application No. 61/691,634, filed Aug. 21, 2012, and U.S. 20140057297, filed Aug. 20, 2013, "Antibodies to Quetiapine Haptens and Use Thereof" (U.S. Provisional Patent Application No. 61/691,598, filed Aug. 21, 2012, and US 20140057305, filed Aug. 20, 2013, "Antibodies to Risperidone Haptens and Use Thereof" (U.S. Provisional Patent Application No. 61/691,615, filed Aug. 21, 2012, and US 20140057301, filed Aug. 20, 2013, "Antibodies to Aripiprazole and Use Thereof" (U.S. Provisional Patent Application No. 61/691,522, filed Aug. 21, 2012, and US 20140057300, filed Aug. 20, 2013, "Antibodies to Olanzapine and Use Thereof" (U.S. Provisional Patent Application No. 61/691,645, filed Aug. 21, 2012, and US 20140057304, filed Aug. 20, 2013, "Antibodies to Quetiapine and Use Thereof" (U.S. Provisional Patent Application No. 61/691,659, filed Aug. 21, 2012, and US 20140057306, filed Aug. 20, 2013, as well as priority applications "Antibodies to Risperidone and Use Thereof" (U.S. Provisional Patent Application No. 61/691,675, filed Aug. 21, 2012, and "Antibodies to Risperidone and Use Thereof" (U.S. Provisional Patent Application No. 61/790,880, filed Mar. 15, 2013, are all incorporated herein by reference in their entireties.

EXAMPLE 1

Antibodies to Aripiprazole

Antibody 17.3 Clone 3D7

The hybridoma designated 17.3 clone 3D7 secretes a monoclonal antibody (mAb) specific for aripiprazole. The antibody is designated 17.3 clone 3D7. The nucleotide sequence of mAb 17.3 clone 3D7's light chain variable region (V_L) is designated SEQ ID NO:41 and that of the heavy chain variable region (V_H) is designated SEQ ID NO:42. Within mAb 17.3 clone 3D7's V_L , nucleotides 136-165 of SEQ ID NO:41 represent the first complementarity determining region (CDR1); nucleotides 211-231 of SEQ ID NO:41 represent the second complementarity determining region (CDR2); and nucleotides 328-354 of SEQ ID NO:41 represent the third complementarity determining region (CDR3). Within mAb 17.3 clone 3D7's V_H , nucleotides 133-162 of SEQ ID NO:42 represent the first complementarity determining region (CDR1); nucleotides 205-255 of SEQ ID NO:42 represent the second complementarity determining region (CDR2); and nucleotides 352-375 of SEQ ID NO:42 represent the third complementarity determining region (CDR3).

The corresponding predicted amino acid sequences of mAb 17.3 clone 3D7's variable chain regions were also determined, and are designated SEQ ID NO:43 (light chain) and SEQ ID NO:44 (heavy chain). Within mAb 17.3 clone 3D7's V_L , amino acid residues 46-55 of SEQ ID NO:43 represent the first complementarity determining region (CDR1); amino acid residues 71-77 of SEQ ID NO:43 represent the second complementarity determining region (CDR2); and amino acid residues 110-118 of SEQ ID NO:43 represent the third complementarity determining region

14

(CDR3). Within mAb 17.3 clone 3D7's V_H , amino acid residues 45-54 of SEQ ID NO:44 represent the first complementarity determining region (CDR1); amino acid residues 69-85 of SEQ ID NO:44 represent the second complementarity determining region (CDR2); and amino acid residues 118-125 of SEQ ID NO:44 represent the third complementarity determining region (CDR3).

Antibody 17.3 Clone 5C7 (First)

The hybridoma designated 17.3 clone 5C7 (first) secretes a monoclonal antibody (mAb) specific for aripiprazole. The antibody is designated 17.3 clone 5C7 (first). The nucleotide sequence of mAb 17.3 clone 5C7 (first)'s light chain variable region (V_L) is designated SEQ ID NO:45 and that of the heavy chain variable region (V_H) is designated SEQ ID NO:46. Within mAb 17.3 clone 5C7 (first)'s V_L , nucleotides 130-162 of SEQ ID NO:45 represent the first complementarity determining region (CDR1); nucleotides 208-228 of SEQ ID NO:45 represent the second complementarity determining region (CDR2); and nucleotides 325-351 of SEQ ID NO:45 represent the third complementarity determining region (CDR3). Within mAb 17.3 clone 5C7 (first)'s V_H , nucleotides 133-162 of SEQ ID NO:46 represent the first complementarity determining region (CDR1); nucleotides 205-255 of SEQ ID NO:46 represent the second complementarity determining region (CDR2); and nucleotides 352-378 of SEQ ID NO:46 represent the third complementarity determining region (CDR3).

The corresponding predicted amino acid sequences of mAb 17.3 clone 5C7 (first)'s variable chain regions were also determined, and are designated SEQ ID NO:47 (light chain) and SEQ ID NO:48 (heavy chain). Within mAb 17.3 clone 5C7 (first)'s V_L , amino acid residues 44-54 of SEQ ID NO:47 represent the first complementarity determining region (CDR1); amino acid residues 70-76 of SEQ ID NO:47 represent the second complementarity determining region (CDR2); and amino acid residues 109-117 of SEQ ID NO:47 represent the third complementarity determining region (CDR3). Within mAb 17.3 clone 5C7 (first)'s V_H , amino acid residues 45-54 of SEQ ID NO:48 represent the first complementarity determining region (CDR1); amino acid residues 69-85 of SEQ ID NO:48 represent the second complementarity determining region (CDR2); and amino acid residues 118-126 of SEQ ID NO:48 represent the third complementarity determining region (CDR3).

Antibody 17.3 Clone 5C7 (Second)

The hybridoma designated 17.3 clone 5C7 (second) secretes a monoclonal antibody (mAb) specific for aripiprazole. The antibody is designated 17.3 clone 5C7 (second). The nucleotide sequence of mAb 17.3 clone 5C7 (second)'s light chain variable region (V_L) is designated SEQ ID NO:49 and that of the heavy chain variable region (V_H) is designated SEQ ID NO:50. Within mAb 17.3 clone 5C7 (second)'s V_L , nucleotides 130-174 of SEQ ID NO:49 represent the first complementarity determining region (CDR1); nucleotides 220-240 of SEQ ID NO:49 represent the second complementarity determining region (CDR2); and nucleotides 337-363 of SEQ ID NO:49 represent the third complementarity determining region (CDR3). Within mAb 17.3 clone 5C7 (second)'s V_H , nucleotides 133-162 of SEQ ID NO:50 represent the first complementarity determining region (CDR1); nucleotides 205-255 of SEQ ID NO:50 represent the second complementarity determining region (CDR2); and nucleotides 352-390 of SEQ ID NO:50 represent the third complementarity determining region (CDR3).

The corresponding predicted amino acid sequences of mAb 17.3 clone 5C7 (second)'s variable chain regions were

15

also determined, and are designated SEQ ID NO:51 (light chain) and SEQ ID NO:52 (heavy chain). Within mAb 17.3 clone 5C7 (second)'s V_L , amino acid residues 44-58 of SEQ ID NO:51 represent the first complementarity determining region (CDR1); amino acid residues 74-80 of SEQ ID NO:51 represent the second complementarity determining region (CDR2); and amino acid residues 113-121 of SEQ ID NO:51 represent the third complementarity determining region (CDR3). Within mAb 17.3 clone 5C7 (second)'s V_H , amino acid residues 45-54 of SEQ ID NO:52 represent the first complementarity determining region (CDR1); amino acid residues 69-85 of SEQ ID NO:52 represent the second complementarity determining region (CDR2); and amino acid residues 118-130 of SEQ ID NO:52 represent the third complementarity determining region (CDR3).

Antibody 17.3 Clone 5C7 (Third)

The hybridoma designated 17.3 clone 5C7 (third) secretes a monoclonal antibody (mAb) specific for aripiprazole. The antibody is designated 17.3 clone 5C7 (third). The nucleotide sequence of mAb 17.3 clone 5C7 (third)'s light chain variable region (V_L) is designated SEQ ID NO:53 and that of the heavy chain variable region (V_H) is designated SEQ ID NO:54. Within mAb 17.3 clone 5C7 (third)'s V_L , nucleotides 130-162 of SEQ ID NO:53 represent the first complementarity determining region (CDR1); nucleotides 208-228 of SEQ ID NO:53 represent the second complementarity determining region (CDR2); and nucleotides 325-351 of SEQ ID NO:53 represent the third complementarity determining region (CDR3). Within mAb 17.3 clone 5C7 (third)'s V_H , nucleotides 133-162 of SEQ ID NO:54 represent the first complementarity determining region (CDR1); nucleotides 205-255 of SEQ ID NO:54 represent the second complementarity determining region (CDR2); and nucleotides 352-366 of SEQ ID NO:54 represent the third complementarity determining region (CDR3).

The corresponding predicted amino acid sequences of mAb 17.3 clone 5C7 (third)'s variable chain regions were also determined, and are designated SEQ ID NO:55 (light chain) and SEQ ID NO:56 (heavy chain). Within mAb 17.3 clone 5C7 (third)'s V_L , amino acid residues 44-54 of SEQ ID NO:55 represent the first complementarity determining region (CDR1); amino acid residues 70-76 of SEQ ID NO:55 represent the second complementarity determining region (CDR2); and amino acid residues 109-117 of SEQ ID NO:55 represent the third complementarity determining region (CDR3). Within mAb 17.3 clone 5C7 (third)'s V_H , amino acid residues 45-54 of SEQ ID NO:56 represent the first complementarity determining region (CDR1); amino acid residues 69-85 of SEQ ID NO:56 represent the second complementarity determining region (CDR2); and amino acid residues 118-122 of SEQ ID NO:56 represent the third complementarity determining region (CDR3).

EXAMPLE 2

Antibodies to Olanzapine

Antibody 11.1 Clone 35

The hybridoma designated 11.1 clone 35 secretes a monoclonal antibody (mAb) specific for olanzapine. The antibody is designated 11.1 clone 35. The nucleotide sequence of mAb 11.1 clone 35's light chain variable region (V_L) is designated SEQ ID NO:9 and that of the heavy chain variable region (V_H) is designated SEQ ID NO:10. Within mAb 11.1 clone 35's V_L , nucleotides 130-162 of SEQ ID NO:9 represent the first complementarity determining region (CDR1); nucleotides 208-228 of SEQ ID NO:9 represent the second complementarity determining region (CDR2); and nucleotides 325-351 of SEQ ID NO:9 represent the third complementarity determining region (CDR3). Within mAb 11.1 clone 35's V_H , nucleotides 133-162 of SEQ ID NO:10 represent the first complementarity determining region (CDR1); nucleotides 205-255 of SEQ ID NO:10 represent the second complementarity determining region (CDR2); and nucleotides 352-366 of SEQ ID NO:10 represent the third complementarity determining region (CDR3).

16

(CDR2); and nucleotides 325-351 of SEQ ID NO:9 represent the third complementarity determining region (CDR3). Within mAb 11.1 clone 35's V_H , nucleotides 133-162 of SEQ ID NO:10 represent the first complementarity determining region (CDR1); nucleotides 205-255 of SEQ ID NO:10 represent the second complementarity determining region (CDR2); and nucleotides 352-366 of SEQ ID NO:10 represent the third complementarity determining region (CDR3).

The corresponding predicted amino acid sequences of mAb 11.1 clone 35's variable chain regions were also determined, and are designated SEQ ID NO:11 (light chain) and SEQ ID NO:12 (heavy chain). Within mAb 11.1 clone 35's V_L , amino acid residues 44-54 of SEQ ID NO:11 represent the first complementarity determining region (CDR1); amino acid residues 70-76 of SEQ ID NO:11 represent the second complementarity determining region (CDR2); and amino acid residues 109-117 of SEQ ID NO:11 represent the third complementarity determining region (CDR3). Within mAb 11.1 clone 35's V_H , amino acid residues 45-54 of SEQ ID NO:12 represent the first complementarity determining region (CDR1); amino acid residues 69-85 of SEQ ID NO:12 represent the second complementarity determining region (CDR2); and amino acid residues 118-122 of SEQ ID NO:12 represent the third complementarity determining region (CDR3).

Antibody 11.1 Clone 61

The hybridoma designated 11.1 clone 61 secretes a monoclonal antibody (mAb) specific for olanzapine. The antibody is designated 11.1 clone 61. The nucleotide sequence of mAb 11.1 clone 61's light chain variable region (V_L) is designated SEQ ID NO:13 and that of the heavy chain variable region (V_H) is designated SEQ ID NO:14. Within mAb 11.1 clone 61's V_L , nucleotides 130-162 of SEQ ID NO:13 represent the first complementarity determining region (CDR1); nucleotides 208-228 of SEQ ID NO:13 represent the second complementarity determining region (CDR2); and nucleotides 325-351 of SEQ ID NO:13 represent the third complementarity determining region (CDR3). Within mAb 11.1 clone 61's V_H , nucleotides 133-162 of SEQ ID NO:14 represent the first complementarity determining region (CDR1); nucleotides 205-255 of SEQ ID NO:14 represent the second complementarity determining region (CDR2); and nucleotides 352-366 of SEQ ID NO:14 represent the third complementarity determining region (CDR3).

The corresponding predicted amino acid sequences of mAb 11.1 clone 61's variable chain regions were also determined, and are designated SEQ ID NO:15 (light chain) and SEQ ID NO:16 (heavy chain). Within mAb 11.1 clone 61's V_L , amino acid residues 44-54 of SEQ ID NO:15 represent the first complementarity determining region (CDR1); amino acid residues 70-76 of SEQ ID NO:15 represent the second complementarity determining region (CDR2); and amino acid residues 109-117 of SEQ ID NO:15 represent the third complementarity determining region (CDR3). Within mAb 11.1 clone 61's V_H , amino acid residues 45-54 of SEQ ID NO:16 represent the first complementarity determining region (CDR1); amino acid residues 69-85 of SEQ ID NO:16 represent the second complementarity determining region (CDR2); and amino acid residues 118-122 of SEQ ID NO:16 represent the third complementarity determining region (CDR3).

Antibody 15.5 Clone 3F11 (First)

The hybridoma designated 15.5 clone 3F11 (first) secretes a monoclonal antibody (mAb) specific for olanzapine. The antibody is designated 15.5 clone 3F11 (first). The nucleotide

tide sequence of mAb 15.5 clone 3F11 (first)'s light chain variable region (V_L) is designated SEQ ID NO:29 and that of the heavy chain variable region (V_H) is designated SEQ ID NO:30. Within mAb 15.5 clone 3F11 (first)'s V_L , nucleotides 130-162 of SEQ ID NO:29 represent the first complementarity determining region (CDR1); nucleotides 208-228 of SEQ ID NO:29 represent the second complementarity determining region (CDR2); and nucleotides 325-351 of SEQ ID NO:29 represent the third complementarity determining region (CDR3). Within mAb 15.5 clone 3F11 (first)'s V_H , nucleotides 130-162 of SEQ ID NO:30 represent the first complementarity determining region (CDR1); nucleotides 205-252 of SEQ ID NO:30 represent the second complementarity determining region (CDR2); and nucleotides 355-381 of SEQ ID NO:30 represent the third complementarity determining region (CDR3).

The corresponding predicted amino acid sequences of mAb 15.5 clone 3F11 (first)'s variable chain regions were also determined, and are designated SEQ ID NO:31 (light chain) and SEQ ID NO:32 (heavy chain). Within mAb 15.5 clone 3F11 (first)'s V_L , amino acid residues 44-54 of SEQ ID NO:31 represent the first complementarity determining region (CDR1); amino acid residues 70-76 of SEQ ID NO:31 represent the second complementarity determining region (CDR2); and amino acid residues 109-117 of SEQ ID NO:31 represent the third complementarity determining region (CDR3). Within mAb 15.5 clone 3F11 (first)'s V_H , amino acid residues 44-54 of SEQ ID NO:32 represent the first complementarity determining region (CDR1); amino acid residues 69-84 of SEQ ID NO:32 represent the second complementarity determining region (CDR2); and amino acid residues 119-127 of SEQ ID NO:32 represent the third complementarity determining region (CDR3).

Antibody 15.5 Clone 3F11 (Second)

The hybridoma designated 15.5 clone 3F11 (second) secretes a monoclonal antibody (mAb) specific for olanzapine. The antibody is designated 15.5 clone 3F11 (second). The nucleotide sequence of mAb 15.5 clone 3F11 (second)'s light chain variable region (V_L) is designated SEQ ID NO:33 and that of the heavy chain variable region (V_H) is designated SEQ ID NO:34. Within mAb 15.5 clone 3F11 (second)'s V_L , nucleotides 130-162 of SEQ ID NO:33 represent the first complementarity determining region (CDR1); nucleotides 208-228 of SEQ ID NO:33 represent the second complementarity determining region (CDR2); and nucleotides 325-351 of SEQ ID NO:33 represent the third complementarity determining region (CDR3). Within mAb 15.5 clone 3F11 (second)'s V_H , nucleotides 133-162 of SEQ ID NO:34 represent the first complementarity determining region (CDR1); nucleotides 205-261 of SEQ ID NO:34 represent the second complementarity determining region (CDR2); and nucleotides 358-381 of SEQ ID NO:34 represent the third complementarity determining region (CDR3).

The corresponding predicted amino acid sequences of mAb 15.5 clone 3F11 (second)'s variable chain regions were also determined, and are designated SEQ ID NO:35 (light chain) and SEQ ID NO:36 (heavy chain). Within mAb 15.5 clone 3F11 (second)'s V_L , amino acid residues 44-54 of SEQ ID NO:35 represent the first complementarity determining region (CDR1); amino acid residues 70-76 of SEQ ID NO:35 represent the second complementarity determining region (CDR2); and amino acid residues 109-117 of SEQ ID NO:35 represent the third complementarity determining region (CDR3). Within mAb 15.5 clone 3F11 (second)'s V_H , amino acid residues 45-54 of SEQ ID NO:36 represent the first complementarity determining region

(CDR1); amino acid residues 69-87 of SEQ ID NO:36 represent the second complementarity determining region (CDR2); and amino acid residues 120-127 of SEQ ID NO:36 represent the third complementarity determining region (CDR3).

Antibody 15.5 Sub-Clone 4G9-1

The hybridoma designated 15.5 sub-clone 4G9-1 secretes a monoclonal antibody (mAb) specific for olanzapine. The antibody is designated 15.5 sub-clone 4G9-1. The nucleotide sequence of mAb 15.5 sub-clone 4G9-1's light chain variable region (V_L) is designated SEQ ID NO:37 and that of the heavy chain variable region (V_H) is designated SEQ ID NO:38. Within mAb 15.5 sub-clone 4G9-1's V_L , nucleotides 130-162 of SEQ ID NO:37 represent the first complementarity determining region (CDR1); nucleotides 208-228 of SEQ ID NO:37 represent the second complementarity determining region (CDR2); and nucleotides 325-351 of SEQ ID NO:37 represent the third complementarity determining region (CDR3). Within mAb 15.5 sub-clone 4G9-1's V_H , nucleotides 130-162 of SEQ ID NO:38 represent the first complementarity determining region (CDR1); nucleotides 205-252 of SEQ ID NO:38 represent the second complementarity determining region (CDR2); and nucleotides 358-381 of SEQ ID NO:38 represent the third complementarity determining region (CDR3).

The corresponding predicted amino acid sequences of mAb 15.5 sub-clone 4G9-1's variable chain regions were also determined, and are designated SEQ ID NO:39 (light chain) and SEQ ID NO:40 (heavy chain). Within mAb 15.5 sub-clone 4G9-1's V_L , amino acid residues 44-54 of SEQ ID NO:39 represent the first complementarity determining region (CDR1); amino acid residues 70-76 of SEQ ID NO:39 represent the second complementarity determining region (CDR2); and amino acid residues 109-117 of SEQ ID NO:39 represent the third complementarity determining region (CDR3). Within mAb 15.5 sub-clone 4G9-1's V_H , amino acid residues 44-54 of SEQ ID NO:40 represent the first complementarity determining region (CDR1); amino acid residues 69-84 of SEQ ID NO:40 represent the second complementarity determining region (CDR2); and amino acid residues 120-127 of SEQ ID NO:40 represent the third complementarity determining region (CDR3).

EXAMPLE 3

Antibodies to Quetiapine

Antibody 13.2 Sub-Clone 89-3 (First)

The hybridoma designated 13.2 sub-clone 89-3 (first) secretes a monoclonal antibody (mAb) specific for quetiapine. The antibody is designated 13.2 sub-clone 89-3 (first). The nucleotide sequence of mAb 13.2 sub-clone 89-3 (first)'s light chain variable region (V_L) is designated SEQ ID NO:17 and that of the heavy chain variable region (V_H) is designated SEQ ID NO:18. Within mAb 13.2 sub-clone 89-3 (first)'s V_L , nucleotides 127-174 of SEQ ID NO:17 represent the first complementarity determining region (CDR1); nucleotides 220-240 of SEQ ID NO:17 represent the second complementarity determining region (CDR2); and nucleotides 337-363 of SEQ ID NO:17 represent the third complementarity determining region (CDR3). Within mAb 13.2 sub-clone 89-3 (first)'s V_H , nucleotides 133-162 of SEQ ID NO:18 represent the first complementarity determining region (CDR1); nucleotides 205-255 of SEQ ID NO:18 represent the second complementarity determining region (CDR2); and nucleotides 352-387 of SEQ ID NO:18 represent the third complementarity determining region (CDR3).

19

The corresponding predicted amino acid sequences of mAb 13.2 sub-clone 89-3 (first)'s variable chain regions were also determined, and are designated SEQ ID NO:19 (light chain) and SEQ ID NO:20 (heavy chain). Within mAb 13.2 sub-clone 89-3 (first)'s V_L , amino acid residues 43-58 of SEQ ID NO:19 represent the first complementarity determining region (CDR1); amino acid residues 74-80 of SEQ ID NO:19 represent the second complementarity determining region (CDR2); and amino acid residues 113-121 of SEQ ID NO:19 represent the third complementarity determining region (CDR3). Within mAb 13.2 sub-clone 89-3 (first)'s V_H , amino acid residues 45-54 of SEQ ID NO:20 represent the first complementarity determining region (CDR1); amino acid residues 69-85 of SEQ ID NO:20 represent the second complementarity determining region (CDR2); and amino acid residues 118-129 of SEQ ID NO:20 represent the third complementarity determining region (CDR3).

Antibody 13.2 Sub-Clone 89-3 (Second)

The hybridoma designated 13.2 sub-clone 89-3 (second) secretes a monoclonal antibody (mAb) specific for quetiapine. The antibody is designated 13.2 sub-clone 89-3 (second). The nucleotide sequence of mAb 13.2 sub-clone 89-3 (second)'s light chain variable region (V_L) is designated SEQ ID NO:21 and that of the heavy chain variable region (V_H) is designated SEQ ID NO:22. Within mAb 13.2 sub-clone 89-3 (second)'s V_L , nucleotides 127-174 of SEQ ID NO:21 represent the first complementarity determining region (CDR1); nucleotides 220-240 of SEQ ID NO:21 represent the second complementarity determining region (CDR2); and nucleotides 337-363 of SEQ ID NO:21 represent the third complementarity determining region (CDR3). Within mAb 13.2 sub-clone 89-3 (second)'s V_H , nucleotides 133-162 of SEQ ID NO:22 represent the first complementarity determining region (CDR1); nucleotides 205-255 of SEQ ID NO:22 represent the second complementarity determining region (CDR2); and nucleotides 367-387 of SEQ ID NO:22 represent the third complementarity determining region (CDR3).

The corresponding predicted amino acid sequences of mAb 13.2 sub-clone 89-3 (second)'s variable chain regions were also determined, and are designated SEQ ID NO:23 (light chain) and SEQ ID NO:24 (heavy chain). Within mAb 13.2 sub-clone 89-3 (second)'s V_L , amino acid residues 43-58 of SEQ ID NO:23 represent the first complementarity determining region (CDR1); amino acid residues 74-80 of SEQ ID NO:23 represent the second complementarity determining region (CDR2); and amino acid residues 113-121 of SEQ ID NO:23 represent the third complementarity determining region (CDR3). Within mAb 13.2 sub-clone 89-3 (second)'s V_H , amino acid residues 45-54 of SEQ ID NO:24 represent the first complementarity determining region (CDR1); amino acid residues 69-85 of SEQ ID NO:24 represent the second complementarity determining region (CDR2); and amino acid residues 123-129 of SEQ ID NO:24 represent the third complementarity determining region (CDR3).

Antibody 13.2 Sub-Clone 89-5

The hybridoma designated 13.2 sub-clone 89-5 secretes a monoclonal antibody (mAb) specific for quetiapine. The antibody is designated 13.2 sub-clone 89-5. The nucleotide sequence of mAb 13.2 sub-clone 89-5's light chain variable region (V_L) is designated SEQ ID NO:25 and that of the heavy chain variable region (V_H) is designated SEQ ID NO:26. Within mAb 13.2 sub-clone 89-5's V_L , nucleotides 127-174 of SEQ ID NO:25 represent the first complementarity determining region (CDR1); nucleotides 220-240 of

20

SEQ ID NO:25 represent the second complementarity determining region (CDR2); and nucleotides 337-363 of SEQ ID NO:25 represent the third complementarity determining region (CDR3). Within mAb 13.2 sub-clone 89-5's V_H , nucleotides 133-162 of SEQ ID NO:26 represent the first complementarity determining region (CDR1); nucleotides 205-255 of SEQ ID NO:26 represent the second complementarity determining region (CDR2); and nucleotides 367-387 of SEQ ID NO:26 represent the third complementarity determining region (CDR3).

The corresponding predicted amino acid sequences of mAb 13.2 sub-clone 89-5's variable chain regions were also determined, and are designated SEQ ID NO:27 (light chain) and SEQ ID NO:28 (heavy chain). Within mAb 13.2 sub-clone 89-5's V_L , amino acid residues 43-58 of SEQ ID NO:27 represent the first complementarity determining region (CDR1); amino acid residues 74-80 of SEQ ID NO:27 represent the second complementarity determining region (CDR2); and amino acid residues 113-121 of SEQ ID NO:27 represent the third complementarity determining region (CDR3). Within mAb 13.2 sub-clone 89-5's V_H , amino acid residues 45-54 of SEQ ID NO:28 represent the first complementarity determining region (CDR1); amino acid residues 69-85 of SEQ ID NO:28 represent the second complementarity determining region (CDR2); and amino acid residues 123-129 of SEQ ID NO:28 represent the third complementarity determining region (CDR3).

EXAMPLE 4

Antibodies to Risperidone/Paliperidone

Antibody 5_9

The hybridoma designated 5_9 secretes a monoclonal antibody (mAb) specific for risperidone (and its metabolite paliperidone). The antibody is designated 5-9. The nucleotide sequence of mAb 5-9's light chain variable region (V_L) is designated SEQ ID NO:1 and that of the heavy chain variable region (V_H) is designated SEQ ID NO:2. Within mAb 5-9's V_L , nucleotides 130-180 of SEQ ID NO:1 represent the first complementarity determining region (CDR1); nucleotides 226-246 of SEQ ID NO:1 represent the second complementarity determining region (CDR2); and nucleotides 343-369 of SEQ ID NO:1 represent the third complementarity determining region (CDR3). Within mAb 5-9's V_H , nucleotides 133-162 of SEQ ID NO:2 represent the first complementarity determining region (CDR1); nucleotides 205-255 of SEQ ID NO:2 represent the second complementarity determining region (CDR2); and nucleotides 352-366 of SEQ ID NO:2 represent the third complementarity determining region (CDR3).

The corresponding predicted amino acid sequences of mAb 5-9's variable chain regions were also determined, and are designated SEQ ID NO:3 (light chain) and SEQ ID NO:4 (heavy chain). Within mAb 5-9's V_L , amino acid residues 44-60 of SEQ ID NO:3 represent the first complementarity determining region (CDR1); amino acid residues 76-82 of SEQ ID NO:3 represent the second complementarity determining region (CDR2); and amino acid residues 115-123 of SEQ ID NO:3 represent the third complementarity determining region (CDR3). Within mAb 5-9's V_H , amino acid residues 45-54 of SEQ ID NO:4 represent the first complementarity determining region (CDR1); amino acid residues 69-85 of SEQ ID NO:4 represent the second complementarity determining region (CDR2); and amino acid residues 118-122 of SEQ ID NO:4 represent the third complementarity determining region (CDR3).

21

Antibody 5_5

The hybridoma designated 5_5 secretes a monoclonal antibody (mAb) specific for risperidone (and its metabolite paliperidone). The antibody is designated 5-5. The nucleotide sequence of mAb 5-5's light chain variable region (V_L) is designated SEQ ID NO:5 and that of the heavy chain variable region (V_H) is designated SEQ ID NO:6. Within mAb 5-5's V_L , nucleotides 130-180 of SEQ ID NO:5 represent the first complementarity determining region (CDR1); nucleotides 226-246 of SEQ ID NO:5 represent the second complementarity determining region (CDR2); and nucleotides 343-369 of SEQ ID NO:5 represent the third complementarity determining region (CDR3). Within mAb 5-9's V_H , nucleotides 133-162 of SEQ ID NO:6 represent the first complementarity determining region (CDR1); nucleotides 205-255 of SEQ ID NO:6 represent the second complementarity determining region (CDR2); and nucleotides 352-366 of SEQ ID NO:6 represent the third complementarity determining region (CDR3).

22

residues 45-54 of SEQ ID NO:8 represent the first complementarity determining region (CDR1); amino acid residues 69-85 of SEQ ID NO:8 represent the second complementarity determining region (CDR2); and amino acid residues 118-122 of SEQ ID NO:8 represent the third complementarity determining region (CDR3).

EXAMPLE 5

Competitive Immunoassays for Risperidone/Paliperidone and Multiplex Competitive Immunoassay for Aripiprazole, Olanzapine, Quetiapine, and Risperidone/Paliperidone

Following a series of immunizations with paliperidone/risperidone immunogens, mouse tail bleeds were tested for reactivity using an ELISA. Hybridoma supernatants were also tested, and the ELISA data shown in Tables 1 and 2 below shows reactivity of several hybridomas (fusion partner was NSO cells). As shown in Table 2, reactivity of hybridomas 2A5 and 5G11 was seen.

TABLE 1

Dilution	1	2	3	4	5	6	7	8	9	10	11	12
400	1	5	14	39	41	47	58	62	67	72	76	Blank Ag = Bt-Compound#1
1200												
3600												
10800												
400	1	5	14	39	41	47	58	62	67	72	76	
1200												
3600												
10800												
1												
Dilution	1	2	3	4	5	6						
400	3.2562	3.2897	3.3148	3.6038	0.6857	3.3976	Ag = Bt-Cmpd#1					
1200	1.3591	1.4605	1.521	2.3063	0.1476	1.9245						
3600	0.3745	0.4617	0.3733	0.7613	0.038	0.6163						
10800	0.0918	0.1149	0.0908	0.1919	0.0156	0.1834						
Dilution												
	7	8	9	10	11	12						
400	1.3444	2.8639	0.5676	3.5993	2.5144	0.0143	Ag = Bt-Cmpd#1					
1200	0.2841	1.0387	0.1158	2.6921	0.8711	0.0142						
3600	0.0689	0.2742	0.0304	0.9549	0.2236	0.0115						
10800	0.0199	0.0639	0.013	0.2766	0.056	0.0099						
Dilution	1	2	3	4	5	6						
400	3.1217	3.1103	3.1532	3.633	0.6089	3.5705	Ag = Bt-Cmpd#1					
1200	1.2607	1.4817	1.3412	2.1411	0.1327	1.9831						
3600	0.3281	0.4159	0.3819	0.7373	0.0361	0.593						
10800	0.0879	0.1127	0.0929	0.1949	0.0156	0.189						
Dilution	7	8	9	10	11	12						
400	1.1067	2.4001	0.4963	3.4172	2.2432	0.0095	Ag = Bt-Cmpd#1					
1200	0.2691	0.961	0.1027	2.5321	0.7418	0.0098						
3600	0.0723	0.292	0.0284	0.8426	0.2024	0.0079						
10800	0.0229	0.0722	0.0141	0.2393	0.052	0.0086						

The corresponding predicted amino acid sequences of mAb 5-5's variable chain regions were also determined, and are designated SEQ ID NO:7 (light chain) and SEQ ID NO:8 (heavy chain). Within mAb 5-5's V_L , amino acid residues 44-60 of SEQ ID NO:7 represent the first complementarity determining region (CDR1); amino acid residues 76-82 of SEQ ID NO:7 represent the second complementarity determining region (CDR2); and amino acid residues 115-123 of SEQ ID NO:7 represent the third complementarity determining region (CDR3). Within mAb 5-5's V_H , amino acid

TABLE 2

Plate 1			
Dilution	1	2	3
neat	Blank	1C4	6 E6
neat		2A5	7A7
neat		2G10	Empty
neat		3B7	

23

TABLE 2-continued

Plate 1			
Dilution	1	2	3
neat		4D8	
neat		5A12	
neat		5G11	
neat		6C1	
neat	0.0072	0.038	0.0309
neat	0.0077	3.9563	0.1163
neat	0.0069	0.0093	0.0086
neat	0.0076	0.0753	0.0108
neat	0.0114	0.1139	0.0084
neat	0.009	0.0193	0.0123
neat	0.0087	0.2503	0.0085
neat	0.0092	0.086	0.0121

After clones were identified via ELISA reactivity, competition ELISAs were run to approximate affinity and cross-reactivity with similar compounds. FIGS. 1 and 2 show the ELISA cross-reactivity results from hybridoma subclone 5_9. Data shows reactivity to risperidone, as well as its metabolites paliperidone and 7-hydroxyrisperidone.

Supernatants were also tested by competition ELISA to determine if the signals were specific to either risperidone or paliperidone. FIG. 3 shows the results from hybridoma subclone 2A5. Data shows reactivity to both risperidone and paliperidone.

FIG. 4 shows the competitive immunoassay format used on a lateral flow assay device in which the capture antibody, risperidone/paliperidone clone 5-9, was deposited on a chip along with a detection conjugate consisting of risperidone conjugated to a fluorophore. In this competitive format as shown in FIG. 4, a low level of analyte (paliperidone) results in high signal, whereas a high level of analyte (paliperidone) results in low signal. The amount of paliperidone in the sample can be calculated from the loss of fluorescence compared to a control sample with no drug present. A typical

24

FIGS. 7-10 show typical dose response curves for an aripiprazole positive control (sample containing aripiprazole) generated with antibody 5C7 deposited in reaction zone 2 and a labeled aripiprazole competitive binding partner in the conjugate zone (FIG. 7), an olanzapine positive control (sample containing olanzapine) generated with antibody 4G9-1 deposited in reaction zone 4 and a labeled olanzapine competitive binding partner in the conjugate zone (FIG. 8), a quetiapine positive control (sample containing quetiapine) generated with antibody 11 deposited in reaction zone 6 and a labeled quetiapine competitive binding partner in the conjugate zone (FIG. 9), and a risperidone positive control (sample containing risperidone) generated with antibody 5-9 deposited in reaction zone 8 and a labeled risperidone competitive binding partner in the conjugate zone (FIG. 10). The labeled competitive binding partners in the conjugate zone compete with the drugs present in the samples for binding to the antibodies. The amount of label is detected and is an indication of the amount of drug present in the sample (the amount of signal being inversely proportional to the amount of drug in the sample—see FIG. 4).

In order to confirm that conjugates of labeled competitive binding partners do not bind to antibodies deposited in the reaction zones, negative controls were conducted by using samples containing no drugs. Referring to Table 3, a sample containing no aripiprazole is deposited in the sample zone and moves by capillary action through the conjugate zone (this time containing labeled olanzapine, labeled quetiapine, and labeled risperidone, but no labeled aripiprazole) and to the reaction zone. The reaction zone again contains aripiprazole antibody (5C7) in reaction zone 2. Table 3 below shows the results, confirming that there is no dose response and the olanzapine, quetiapine, and risperidone conjugates that move by capillary action through the reaction zone do not bind to the aripiprazole antibody.

TABLE 3

Aripiprazole-Clone 5C7-Math Model 1 (0 ng/mL Conc.)						
Assay-MM	Conj	Reaction Zone	Read Position	Peak Mean Area	Peak Mean Height	Mean Background
ARIP-MM1	OLAN, QUET, RISP	ARIP	2	0.77	1.56	3.99
ARIP-MM1	OLAN, QUET, RISP		4	-0.02	0.06	4.14
ARIP-MM1	OLAN, QUET, RISP		6	0.09	0.10	4.29
ARIP-MM1	OLAN, QUET, RISP		8	0.13	0.12	4.61

Other Conjugates do not bind to Aripiprazole

dose response curve generated with risperidone/paliperidone clone 5-9 is shown in FIG. 5.

FIG. 6 shows the chip design of a lateral flow assay device according to one embodiment of the subject invention. The device includes a zone or area for receiving the sample, a conjugate zone (which contains desired labeled competitive binding partner(s)), and a reaction zone (eight areas within the reaction zone are indicated; each area can contain a separate desired antibody). Sample flows from the sample zone through the conjugate zone and to the reaction zone.

Referring to Table 4, a sample containing no olanzapine is deposited in the sample zone and moves by capillary action through the conjugate zone (this time containing labeled aripiprazole, labeled quetiapine, and labeled risperidone, but no labeled olanzapine) and to the reaction zone. The reaction zone again contains olanzapine antibody (4G9-1) in reaction zone 4. Table 4 below shows the results, confirming that there is no dose response and the aripiprazole, quetiapine, and risperidone conjugates that move by capillary action through the reaction zone do not bind to the olanzapine antibody.

TABLE 4

OLAN-Clone 4G9-1-Math Model 1 (0 ng/mL Conc.)						
Assay-MM	Conj	Reaction Zone	Read Position	Peak Mean Area	Peak Mean Height	Mean Background
OLAN-MM1	ARIP, QUET, RISP	OLAN	2	-0.03	0.05	4.38
OLAN-MM1	ARIP, QUET, RISP		4	0.74	1.10	4.56
OLAN-MM1	ARIP, QUET, RISP		6	0.06	0.09	4.79
OLAN-MM1	ARIP, QUET, RISP		8	0.11	0.13	5.17

Other Conjugates do not bind to Olanzapine

Referring to Table 5, a sample containing no quetiapine is deposited in the sample zone and moves by capillary action through the conjugate zone (this time containing labeled aripiprazole, labeled olanzapine, and labeled risperidone, but no labeled quetiapine) and to the reaction zone. The reaction zone again contains quetiapine antibody (11) in reaction zone 6. Table 5 below shows the results, confirming that there is no dose response and the aripiprazole, olanzapine, and risperidone conjugates that move by capillary action through the reaction zone do not bind to the quetiapine antibody.

TABLE 5

Quetiapine-Clone 11-Math Model 1 (0 ng/mL Conc.)						
Assay-MM	Conj	Reaction Zone	Read Position	Peak Mean Area	Peak Mean Height	Mean Background
QUET-MM1	ARIP, OLAN, RISP	QUET	2	-0.01	0.07	3.85
QUET-MM1	ARIP, OLAN, RISP		4	0.01	0.12	4.01
QUET-MM1	ARIP, OLAN, RISP		6	0.03	0.08	4.24
QUET-MM1	ARIP, OLAN, RISP		8	0.04	0.07	4.56

Other Conjugates do not bind to Quetiapine

Referring to Table 6, a sample containing no risperidone is deposited in the sample zone and moves by capillary action through the conjugate zone (this time containing labeled aripiprazole, labeled olanzapine, and labeled quetiapine, but no labeled risperidone) and to the reaction zone. The reaction zone again contains risperidone antibody (5-9) in reaction zone 8. Table 6 below shows the results, confirming that there is no dose response and the aripiprazole, olanzapine, and quetiapine conjugates that move by capillary action through the reaction zone do not bind to the risperidone antibody.

TABLE 6

Risperidone-Clone 5-9-Math Model 1 (0 ng/mL Conc.)						
Assay-MM	Conj	Reaction Zone	Read Position	Peak Mean Area	Peak Mean Height	Mean Background
RISP-MM1	ARIP, OLAN, QUET	RISP	2	0.02	0.11	7.43
RISP-MM1	ARIP, OLAN, QUET		4	0.05	0.14	7.73
RISP-MM1	ARIP, OLAN, QUET		6	0.20	0.19	8.11
RISP-MM1	ARIP, OLAN, QUET		8	1.97	3.23	8.85

Other Conjugates do not bind to Risperidone

In order to confirm that conjugates of labeled competitive binding partners bind only to their respective antibodies deposited in the reaction zones, additional negative controls were conducted by again using samples containing no drugs. Referring to Table 7, a sample containing no aripiprazole is deposited in the sample zone and moves by capillary action through the conjugate zone (this time containing labeled

aripiprazole) and to the reaction zone. The reaction zone again contains aripiprazole antibody (5C7) in reaction zone 2, as well as olanzapine antibody (4G9-1) in reaction zone 4, quetiapine antibody (11) in reaction zone 6, and risperidone antibody (5-9) in reaction zone 8. Table 7 below shows the results, confirming that there is no dose response except to the aripiprazole antibody 5C7 (in reaction zone 2).

TABLE 7

Aripiprazole-Clone 5C7-Math Model 1 (0 ng/mL Conc.)						
Assay-MM	Conj	Reaction Zone	Read Position	Peak Mean Area	Peak Mean Height	Mean Background
ARIP-MM1	ARIP, OLAN, QUET, RISP	ARIP	2	60.34	97.53	5.44
ARIP-MM1	ARIP, OLAN, QUET, RISP		4	2.86	3.91	11.66
ARIP-MM1	ARIP, OLAN, QUET, RISP		6	1.12	1.23	11.03
ARIP-MM1	ARIP, OLAN, QUET, RISP		8	3.14	4.19	12.94

Only the Aripiprazole Reaction Zone is binding

Referring to Table 8, a sample containing no olanzapine is deposited in the sample zone and moves by capillary action through the conjugate zone (this time containing labeled olanzapine) and to the reaction zone. The reaction zone again contains aripiprazole antibody (5C7) in reaction zone 2, as well as olanzapine antibody (4G9-1) in reaction zone 4, quetiapine antibody (11) in reaction zone 6, and risperidone antibody (5-9) in reaction zone 8. Table 8 below shows the results, confirming that there is no dose response except to the olanzapine antibody 4G9-1 (in reaction zone 4).

TABLE 8

OLAN-Clone 4G9-1-Math Model 1 (0 ng/mL Conc.)						
Assay-MM	Conj	Reaction Zone	Read Position	Peak Mean Area	Peak Mean Height	Mean Background
OLAN-MM1	ARIP, OLAN, QUET, RISP	OLAN	2	0.02	0.08	4.86
OLAN-MM1	ARIP, OLAN, QUET, RISP		4	34.23	51.80	5.39
OLAN-MM1	ARIP, OLAN, QUET, RISP		6	0.22	0.32	5.39
OLAN-MM1	ARIP, OLAN, QUET, RISP		8	0.15	0.17	5.59

Only the Olanzapine Reaction Zone is binding

Referring to Table 9, a sample containing no quetiapine is deposited in the sample zone and moves by capillary action through the conjugate zone (this time containing labeled quetiapine) and to the reaction zone. The reaction zone again contains aripiprazole antibody (5C7) in reaction zone 2, as well as olanzapine antibody (4G9-1) in reaction zone 4, quetiapine antibody (11) in reaction zone 6, and risperidone antibody (5-9) in reaction zone 8. Table 9 below shows the results, confirming that there is no dose response except to the quetiapine antibody 11 (in reaction zone 6).

TABLE 9

Quetiapine-Clone 11-Math Model 1 (0 ng/mL Conc.)						
Assay-MM	Conj	Reaction Zone	Read Position	Peak Mean Area	Peak Mean Height	Mean Background
QUET-MM1	ARIP, OLAN, QUET, RISP	QUET	2	0.13	0.41	10.02
QUET-MM1	ARIP, OLAN, QUET, RISP		4	0.08	0.23	10.47
QUET-MM1	ARIP, OLAN, QUET, RISP		6	140.35	181.33	7.91
QUET-MM1	ARIP, OLAN, QUET, RISP		8	1.58	2.61	11.53

Only the Quetiapine Reaction Zone is binding

Referring to Table 10, a sample containing no risperidone is deposited in the sample zone and moves by capillary action through the conjugate zone (this time containing labeled risperidone) and to the reaction zone. The reaction zone again contains aripiprazole antibody (5C7) in reaction zone 2, as well as olanzapine antibody (4G9-1) in reaction

zone 4, quetiapine antibody (11) in reaction zone 6, and risperidone antibody (5-9) in reaction zone 8. Table 10 below shows the results, confirming that there is no dose response except to the risperidone antibody 5-9 (in reaction zone 8).

TABLE 10

Risperidone-Clone 5-9-Math Model 1 (0 ng/mL Conc.)						
Assay-MM	Conj	Reaction Zone	Read Position	Peak Mean Area	Peak Mean Height	Mean Background
RISP-MM1	ARIP, OLAN, QUET, RISP		2	1.03	1.51	9.07
RISP-MM1	ARIP, OLAN, QUET, RISP		4	0.65	0.91	9.60
RISP-MM1	ARIP, OLAN, QUET, RISP		6	2.61	6.39	10.48
RISP-MM1	ARIP, OLAN, QUET, RISP	RISP	8	55.98	100.91	11.58

Only the Risperidone Reaction Zone is binding

The results shown above confirm that conjugates of labeled competitive binding partners bind only to their respective antibodies in the reaction zone.

FIGS. 11-14 show typical dose response curves in specific antibody reaction zones, and proof of dose response low/high concentration for each specific assay in the presence of other conjugates. In FIG. 11, a sample containing aripiprazole is deposited in the sample zone and moves by capillary action through the conjugate zone (this time containing labeled aripiprazole, labeled olanzapine, labeled quetiapine, and labeled risperidone) and to the reaction zone. The reaction zone again contains aripiprazole antibody (5C7) in reaction zone 2. A typical dose response curve was generated as is shown in FIG. 11 only for aripiprazole, and not for olanzapine, quetiapine, or risperidone.

In FIG. 12, a sample containing olanzapine is deposited in the sample zone and moves by capillary action through the conjugate zone (this time containing labeled aripiprazole, labeled olanzapine, labeled quetiapine, and labeled risperidone) and to the reaction zone. The reaction zone again contains olanzapine antibody (4G9-1) in reaction zone 4. A typical dose response curve was generated as is shown in FIG. 12 only for olanzapine, and not for aripiprazole, quetiapine, or risperidone.

In FIG. 13, a sample containing quetiapine is deposited in the sample zone and moves by capillary action through the conjugate zone (this time containing labeled aripiprazole, labeled olanzapine, labeled quetiapine, and labeled risperidone) and to the reaction zone. The reaction zone again contains quetiapine antibody (11) in reaction zone 6. A typical dose response curve was generated as is shown in FIG. 13 only for quetiapine, and not for aripiprazole, olanzapine, or risperidone.

In FIG. 14, a sample containing risperidone is deposited in the sample zone and moves by capillary action through the conjugate zone (this time containing labeled aripiprazole, labeled olanzapine, labeled quetiapine, and labeled

risperidone) and to the reaction zone. The reaction zone again contains risperidone antibody (5-9) in reaction zone 8. A typical dose response curve was generated as is shown in FIG. 14 only for risperidone, and not for aripiprazole, olanzapine, or quetiapine.

FIGS. 15-18 show typical dose response curves for each assay in the presence of other conjugates and antibodies. In FIG. 15, a sample containing aripiprazole is deposited in the sample zone and moves by capillary action through the conjugate zone (again containing labeled aripiprazole, labeled olanzapine, labeled quetiapine, and labeled risperidone) and to the reaction zone. The reaction zone again contains aripiprazole antibody (5C7) in reaction zone 2, as well as olanzapine antibody (4G9-1) in reaction zone 4, quetiapine antibody (11) in reaction zone 6, and risperidone antibody (5-9) in reaction zone 8. A typical dose response curve was generated for aripiprazole, as is shown in FIG. 15. When a sample containing olanzapine was deposited in the sample zone of this chip, a typical dose response curve was generated for olanzapine as shown in FIG. 16. When a sample containing quetiapine was deposited in the sample zone of this chip, a typical dose response curve for quetiapine was generated as shown in FIG. 17. When a sample containing risperidone was deposited in the sample zone of this chip, a typical dose response curve for risperidone was generated as shown in FIG. 18.

FIGS. 19-22 show comparisons of dose response curves generated as positive controls (FIGS. 7-10) to dose response curves generated in the multiplex format (FIGS. 15-18). The comparison for aripiprazole is shown in FIG. 19; for olanzapine in FIG. 20; for quetiapine in FIG. 21; and for risperidone in FIG. 22. These figures show that the positive control curves are similar to the multiplex curves.

These data show that a lateral flow assay device of the subject invention can be used to detect multiple anti-psychotic drugs using a single sample from a patient on one portable, point-of-care device.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 56

<210> SEQ ID NO 1

<211> LENGTH: 399

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 1

atggaatcac agactcaggt cctcatgtcc ctgtgctct ggatatctgg tacctatggg 60

gacattgtga tgacacagtc tccatcctcc ctgagtggtg caacaggaga taaggtcact 120

-continued

```

atgagctgca agtccagtca gagtctgttc aacagtagaa accaaaagag ctacttggcc 180
tggtaccagc agaagccatg gcagcctcct aaactgctga tctacggggc atccactagg 240
gaatctgggg tcctgatcg cttcacaggc agtggatctg gaacagatctt cactctcacc 300
atcagcagtg tgcaggctga agacctggca atttattact gtcagaatga ttatagttat 360
ccattcacgt tcggcacggg gacaaaattg gaaataaga 399

```

```

<210> SEQ ID NO 2
<211> LENGTH: 399
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

```

```

<400> SEQUENCE: 2

```

```

atgggattca gcaggatctt tctcttctc ctgtcagtaa ctacaggtgt ccactcccag 60
gctttttctac aacaatctgg ggtgagctg gtgaggcctg gggcctcagt gaagatgtcc 120
tgcaaggcct ctggtctccac atttaccagt tacaatatac actgggtcaa gcagacacct 180
agacagggcc tggaatggat tggagctatt tatccaggaa atggtgatac ttctacaat 240
cagaagtcca agggcagggc cacactgact atagacaaat cctccagcac agcctacatg 300
cagctcagca gcctgacatc tgaagactct gcggtctatt tctgtgctaa ctggggcttt 360
gagtactggg gtcaaggcac cactctctca gtctctca 399

```

```

<210> SEQ ID NO 3
<211> LENGTH: 133
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

```

```

<400> SEQUENCE: 3

```

```

Met Glu Ser Gln Thr Gln Val Leu Met Ser Leu Leu Leu Trp Ile Ser
1      5      10      15
Gly Thr Tyr Gly Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser
20     25     30
Val Ala Thr Gly Asp Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser
35     40     45
Leu Phe Asn Ser Arg Asn Gln Lys Ser Tyr Leu Ala Trp Tyr Gln Gln
50     55     60
Lys Pro Trp Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg
65     70     75     80
Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp
85     90     95
Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Ile Tyr
100    105    110
Tyr Cys Gln Asn Asp Tyr Ser Tyr Pro Phe Thr Phe Gly Thr Gly Thr
115    120    125
Lys Leu Glu Ile Arg
130

```

```

<210> SEQ ID NO 4
<211> LENGTH: 133
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

```

-continued

<400> SEQUENCE: 4

```

Met Gly Phe Ser Arg Ile Phe Leu Phe Leu Leu Ser Val Thr Thr Gly
1      5      10      15
Val His Ser Gln Ala Phe Leu Gln Gln Ser Gly Ala Glu Leu Val Arg
20     25     30
Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Ser Thr Phe
35     40     45
Thr Ser Tyr Asn Ile His Trp Val Lys Gln Thr Pro Arg Gln Gly Leu
50     55     60
Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn
65     70     75     80
Gln Lys Phe Lys Gly Arg Ala Thr Leu Thr Ile Asp Lys Ser Ser Ser
85     90     95
Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
100    105    110
Tyr Phe Cys Ala Asn Trp Gly Phe Glu Tyr Trp Gly Gln Gly Thr Thr
115    120    125
Leu Ser Val Ser Ser
130

```

<210> SEQ ID NO 5

<211> LENGTH: 399

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 5

```

atggaatcac agactcaggt cctcatgtcc ctgctgctct ggatatcttg tacctatggg      60
gacattgtga tgacacagtc tccatcctcc ctgagtgtgg caacaggaga taaggtcact      120
atgagctgca agtccagtc gagtctgttc aacagtagaa accaaaagag ctacttggcc      180
tggtaccagc agaagccatg gcagcctcct aaactgctga tctacggggc atccactagg      240
gaatctgggg tccctgatcg cttcacaggc agtggatctg gaacagattt cactctcacc      300
atcagcagtg tgcaggctga agacctggca atttattact gtcagaatga ttatagttaa      360
ccattcacgt tcggcacggg gacaaaattg gaaataaga                               399

```

<210> SEQ ID NO 6

<211> LENGTH: 399

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 6

```

atgggattca gcaggatctt tctcttctc ctgtcagtaa ctacaggtgt cactcccag      60
gtttttctac aacaatctgg ggctgagctg gtgaggcctg gggcctcagt gaagatgtcc      120
tgcaaggcct ctggctccac atttaccagt tacaatatac actgggtcaa gcagacacct      180
agacagggcc tggaatggat tggagctatt tatccaggaa atggtgatac ttctacaat      240
cagaagttaa agggcagggc cacactgact atagacaaat cctccagcac agcctacatg      300
cagctcagca gcctgacatc tgaagactct gcggtctatt tctgtgctaa ctggggcttt      360
gagtactggg gtcaaggcac cactctctca gtctctca                               399

```

<210> SEQ ID NO 7

-continued

```

<211> LENGTH: 133
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 7

Met Glu Ser Gln Thr Gln Val Leu Met Ser Leu Leu Trp Ile Ser
1          5          10          15
Gly Thr Tyr Gly Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser
20        25        30
Val Ala Thr Gly Asp Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser
35        40        45
Leu Phe Asn Ser Arg Asn Gln Lys Ser Tyr Leu Ala Trp Tyr Gln Gln
50        55        60
Lys Pro Trp Gln Pro Pro Lys Leu Leu Ile Tyr Gly Ala Ser Thr Arg
65        70        75        80
Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp
85        90        95
Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Ile Tyr
100       105       110
Tyr Cys Gln Asn Asp Tyr Ser Tyr Pro Phe Thr Phe Gly Thr Gly Thr
115       120       125
Lys Leu Glu Ile Arg
130

```

```

<210> SEQ ID NO 8
<211> LENGTH: 133
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 8

Met Gly Phe Ser Arg Ile Phe Leu Phe Leu Leu Ser Val Thr Thr Gly
1          5          10          15
Val His Ser Gln Ala Phe Leu Gln Gln Ser Gly Ala Glu Leu Val Arg
20        25        30
Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Ser Thr Phe
35        40        45
Thr Ser Tyr Asn Ile His Trp Val Lys Gln Thr Pro Arg Gln Gly Leu
50        55        60
Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn
65        70        75        80
Gln Lys Phe Lys Gly Arg Ala Thr Leu Thr Ile Asp Lys Ser Ser Ser
85        90        95
Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
100       105       110
Tyr Phe Cys Ala Asn Trp Gly Phe Glu Tyr Trp Gly Gln Gly Thr Thr
115       120       125
Leu Ser Val Ser Ser
130

```

```

<210> SEQ ID NO 9
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

```

-continued

<400> SEQUENCE: 9

```

atggagtcac agactcaggt ctttgattc gtgttgcctt gggtgtctgg tggagatgga      60
gacattgtga tgaccacgac tcaaaaattc atgtccacat cactaggaga cagggtcagc      120
atcacctgca aggccagtcg gaatgtggga atttatgttt cctgggtatc acagaaacca      180
gggaaatctc ctaaagcact aatttactgg tcttcaaacc gggtcactgg agtcctgat      240
cgtttcacag gcagtggatc tgggacagac ttcactctca ccatcaccga tgtgcagtct      300
gaagacttgg cagattatct ctgtgagcaa tatagcagcg atccgtatac gttcggatcg      360
gggaccaagc tggaaataaa a                                     381

```

<210> SEQ ID NO 10

<211> LENGTH: 399

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 10

```

atggaaagac actggatctt tctcttctg ttgtcagtaa ctgcaggtgt ccactcccag      60
gtccaaactgc agcagctctg ggctgaactg gcaagacctg gggcctcagt gaagatgtcc      120
tgcaagactt ctggctacac cttcactagc gaccggatgc actgggtaat acagaggcct      180
ggacaggggc tggagtggat tggatacatt cttcctagaa atgtttatac taaatacaat      240
aaaaagttca aggacaaggc cacattgact gcagacacat cctccagtat agcctacatc      300
caactgagca gcctgacatc tgaagactct gcagtctatt actgtgtaaa gtctgacggg      360
ggctactggg gccaaaggac cactctcaca gtctcctca                                     399

```

<210> SEQ ID NO 11

<211> LENGTH: 127

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 11

```

Met Glu Ser Gln Thr Gln Val Phe Val Phe Val Leu Leu Trp Leu Ser      15
1           5           10           15
Gly Gly Asp Gly Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser      30
20          25          30
Thr Ser Leu Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asn      45
35          40          45
Val Gly Ile Tyr Val Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro      60
50          55          60
Lys Ala Leu Ile Tyr Trp Ser Ser Asn Arg Phe Thr Gly Val Pro Asp      80
65          70          75          80
Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr      95
85          90          95
Asp Val Gln Ser Glu Asp Leu Ala Asp Tyr Phe Cys Glu Gln Tyr Ser      110
100         105         110
Ser Asp Pro Tyr Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys      125
115         120         125

```

<210> SEQ ID NO 12

<211> LENGTH: 133

<212> TYPE: PRT

-continued

```

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 12

Met Glu Arg His Trp Ile Phe Leu Phe Leu Leu Ser Val Thr Ala Gly
 1             5             10             15

Val His Ser Gln Val Gln Leu Gln Gln Ser Ala Ala Glu Leu Ala Arg
 20             25             30

Pro Gly Ala Ser Val Lys Met Ser Cys Lys Thr Ser Gly Tyr Thr Phe
 35             40             45

Thr Ser Asp Arg Met His Trp Val Ile Gln Arg Pro Gly Gln Gly Leu
 50             55             60

Glu Trp Ile Gly Tyr Ile Leu Pro Arg Asn Val Tyr Thr Lys Tyr Asn
 65             70             75             80

Lys Lys Phe Lys Asp Lys Ala Thr Leu Thr Ala Asp Thr Ser Ser Ser
 85             90             95

Ile Ala Tyr Ile Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
 100            105            110

Tyr Tyr Cys Val Lys Ser Asp Gly Gly Tyr Trp Gly Gln Gly Thr Thr
 115            120            125

Leu Thr Val Ser Ser
 130

```

```

<210> SEQ ID NO 13
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 13

atggagtcac agactcaggt cttgtattc gtgtgtctct ggttgtctgg tggatgga      60
gacattgtga tgaccagtc tcaaaaattc atgtccacat cactaggaga cagggtcagc      120
atcacctgca aggccagtc gaattgtgga atttatgtat cctgggtatca acagaaacca      180
gggaaatctc ctaaagcact aatttattgg gcatcaaacc ggttcaactgg agtcctgat      240
cgcttcacag gcagtggatc tgggacagac ttcactctca ccacaccaa tgtgcagtct      300
gaagacttgg cagaatattt ctgtgaacaa tatagcagcg atccgtatac gttcgatcg      360
gggaccaagc tagaaataaa a                                     381

```

```

<210> SEQ ID NO 14
<211> LENGTH: 399
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 14

atggaaaggc actggtctt tctcttctg ttgtcagtaa ctgcagtggt cactcccag      60
gtccaactgc agcagtctgc ggtgaactg gtaagacctg gggcctcagt gaagatgtcc      120
tgcaagactt ctggctacat cttcactagc gaccggatgc actgggtaaa acagaggcct      180
ggacagggtc tggagtggat tggatacatt attcctagaa atttttatac taaatacaat      240
cagaaattca aggacaaggc cacattgact gcagacacat cctccaatac agcctacatg      300
cagttgagca gcctgacatc tgaagactct gcagtctatt actgtgtgaa atctgacggg      360

```

-continued

gcctactggg gccaaaggac cactctcaca gtctctca

399

<210> SEQ ID NO 15
 <211> LENGTH: 127
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 15

Met Glu Ser Gln Thr Gln Val Phe Val Phe Val Leu Leu Trp Leu Ser
 1 5 10 15

Gly Gly Asp Gly Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser
 20 25 30

Thr Ser Leu Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asn
 35 40 45

Val Gly Ile Tyr Val Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro
 50 55 60

Lys Ala Leu Ile Tyr Trp Ala Ser Asn Arg Phe Thr Gly Val Pro Asp
 65 70 75 80

Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr
 85 90 95

Asn Val Gln Ser Glu Asp Leu Ala Glu Tyr Phe Cys Glu Gln Tyr Ser
 100 105 110

Ser Asp Pro Tyr Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
 115 120 125

<210> SEQ ID NO 16
 <211> LENGTH: 133
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 16

Met Glu Arg His Trp Ile Phe Leu Phe Leu Leu Ser Val Thr Ala Gly
 1 5 10 15

Val His Ser Gln Val Gln Leu Gln Gln Ser Ala Ala Glu Leu Val Arg
 20 25 30

Pro Gly Ala Ser Val Lys Met Ser Cys Lys Thr Ser Gly Tyr Ile Phe
 35 40 45

Thr Ser Asp Arg Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu
 50 55 60

Glu Trp Ile Gly Tyr Ile Ile Pro Arg Asn Phe Tyr Thr Lys Tyr Asn
 65 70 75 80

Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Ala Asp Thr Ser Ser Asn
 85 90 95

Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
 100 105 110

Tyr Tyr Cys Val Lys Ser Asp Gly Ala Tyr Trp Gly Gln Gly Thr Thr
 115 120 125

Leu Thr Val Ser Ser
 130

<210> SEQ ID NO 17
 <211> LENGTH: 393
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:

-continued

<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 17

atgaagttgc ctgtaggct gttggtgctg atgttctgga ttctgcttc cagtagtgat	60
gttgtgatga cccaaactcc actctccctg cctgtcagtc ttggagatca agcctccatc	120
tcttggttggc ctagtacagag ccttgtagac agttatggaa acacctatctt acattggtat	180
ctgcagaagc caggccagtc tccaaagctc ctgatctaca aagtttccaa ccgattttct	240
gggggtcccag acaggttcag tggcagtga tcagggacag atttcacact caagatcagc	300
agagtggagg ctgaggatct gggaatttac ttttgctctc aaactacata tgttccgtat	360
acgttcggat cggggaccaa gctggaaatg aaa	393

<210> SEQ ID NO 18

<211> LENGTH: 420

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 18

atggaatgga cctgggtctt tctcttctc ctgtcagtaa ctgcaggtgt ccactcccag	60
gttcagctgc accagtctgg agctgagctg atgaagcctg gggcctcagt gaagatatcc	120
tgcaaggcta ccggctacac atttagtagg tactggatag agtggataaa acagaggcct	180
ggccatggcc ttgagtggat tggagagttt ctacctggaa gtggaaattc taactacaat	240
gctaaattca agggcaaggc caccttcaact gcagcaacat cctccaacac agcctacatg	300
caactcagca gtgtgacatc tgaagactct gccgtctatt tctgtgcaac ctggtacgat	360
gttaactacc gctatcttat ggactattgg ggtcaaggaa cctcagtcac cgtctctca	420

<210> SEQ ID NO 19

<211> LENGTH: 131

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 19

Met Lys Leu Pro Val Arg Leu Leu Val Leu Met Phe Trp Ile Pro Ala	1 5 10 15
Ser Ser Ser Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val	20 25 30
Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Trp Ser Ser Gln Ser Leu	35 40 45
Val Asp Ser Tyr Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro	50 55 60
Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser	65 70 75 80
Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr	85 90 95
Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Phe Cys	100 105 110
Ser Gln Thr Thr Tyr Val Pro Tyr Thr Phe Gly Ser Gly Thr Lys Leu	115 120 125
Glu Met Lys	130

-continued

```

<210> SEQ ID NO 20
<211> LENGTH: 140
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 20

Met Glu Trp Thr Trp Val Phe Leu Phe Leu Leu Ser Val Thr Ala Gly
1             5             10            15
Val His Ser Gln Val Gln Leu His Gln Ser Gly Ala Glu Leu Met Lys
20            25            30
Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe
35            40            45
Ser Arg Tyr Trp Ile Glu Trp Ile Lys Gln Arg Pro Gly His Gly Leu
50            55            60
Glu Trp Ile Gly Glu Phe Leu Pro Gly Ser Gly Asn Ser Asn Tyr Asn
65            70            75            80
Ala Lys Phe Lys Gly Lys Ala Thr Phe Thr Ala Ala Thr Ser Ser Asn
85            90            95
Thr Ala Tyr Met Gln Leu Ser Ser Val Thr Ser Glu Asp Ser Ala Val
100           105           110
Tyr Phe Cys Ala Thr Trp Tyr Asp Val Asn Tyr Arg Tyr Leu Met Asp
115           120           125
Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
130           135           140

```

```

<210> SEQ ID NO 21
<211> LENGTH: 393
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 21

atgaagtgc ctgttaggct gttggtgctg atgttctgga ttctgcttc cagcagtgat    60
attgtgatga cccaaactcc actctccctg cctgtcagtc ttggagatca agcctccatc    120
tcttgcaggt ctagtcagag ccttgtagc agtaatggga acacctatct acattggtac    180
ctgcagaagc caggccagtc tccaaagctc ctgatctaca aagtttccaa ccgattttct    240
gggggtcccc acagggtcag tggcagtgga tcaggacagc atttcacact caagatcagc    300
agagtggagg ctgaggatct gggagtttat ttctgctctc aaagtagaca tgttccgtat    360
acgttcggat cggggaccaa gctggaataa aaa                                393

```

```

<210> SEQ ID NO 22
<211> LENGTH: 420
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 22

atggaatgga cctgggtctt tctcttctc ctgtcagtaa ccgcaggtgt ccactcccag    60
gttcagctgc agcagtctgg agctgtactg atgaagcctg gggcctcagt gaagatatcc    120
tgcaaggcta ctggctacac attcattagg tactggatag agtgggtaaa gaagaggcct    180
ggacatggcc ttgactggat tggagaaatt ttacctggaa gtggaagttc taactacaat    240

```


-continued

gagaacttca aggtcaaggc cactttcact gtagatactt cctccaacac agcctacatg 300
 caactcaaca gcctgacatc tcaggactct gccgtctatt actgtgcaat ttggtacgat 360
 ggtaattacc gctctcttat ggactactgg ggccaaggaa cctcagtcac cgtctcctca 420

<210> SEQ ID NO 23
 <211> LENGTH: 131
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 23

Met Lys Leu Pro Val Arg Leu Leu Val Leu Met Phe Trp Ile Pro Ala
 1 5 10 15
 Ser Ser Ser Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val
 20 25 30
 Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu
 35 40 45
 Val Arg Ser Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro
 50 55 60
 Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser
 65 70 75 80
 Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
 85 90 95
 Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys
 100 105 110
 Ser Gln Ser Thr His Val Pro Tyr Thr Phe Gly Ser Gly Thr Lys Leu
 115 120 125
 Glu Ile Lys
 130

<210> SEQ ID NO 24
 <211> LENGTH: 140
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 24

Met Glu Trp Thr Trp Val Phe Leu Phe Leu Leu Ser Val Thr Ala Gly
 1 5 10 15
 Val His Ser Gln Val Gln Leu Gln Ser Gly Ala Val Leu Met Lys
 20 25 30
 Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe
 35 40 45
 Ile Arg Tyr Trp Ile Glu Trp Val Lys Lys Arg Pro Gly His Gly Leu
 50 55 60
 Asp Trp Ile Gly Glu Ile Leu Pro Gly Ser Gly Ser Ser Asn Tyr Asn
 65 70 75 80
 Glu Asn Phe Lys Val Lys Ala Thr Phe Thr Val Asp Thr Ser Ser Asn
 85 90 95
 Thr Ala Tyr Met Gln Leu Asn Ser Leu Thr Ser Gln Asp Ser Ala Val
 100 105 110
 Tyr Tyr Cys Ala Ile Trp Tyr Asp Gly Asn Tyr Arg Ser Leu Met Asp
 115 120 125
 Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
 130 135 140

-continued

```

<210> SEQ ID NO 25
<211> LENGTH: 393
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 25
atgaagttgc ctgttaggct gttggtgctg atgtttctgga ttctgtcttc cagcagtgat    60
attgtgatga cccaaactcc actctccctg cctgtcagtc ttggagatca agcctccatc    120
tcttgcaggt ctagtccagag ccttgtacgc agtaatggaa acacctatctt acattgggtac    180
ctgcagaagc caggccagtc tccaaagctc ctgatctaca aagtttccaa ccgattttct    240
ggggtccccc acaggttcag tggcagtgga tcaggacagc atttcacact caagatcagc    300
agagtggagg ctgaggatct gggagtttat ttctgtcttc aaagtacaca tggtccgtat    360
acgttcggat cggggaccaa gctggaataa aaa                                393

```

```

<210> SEQ ID NO 26
<211> LENGTH: 420
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 26
atggaatgga cctgggtctt tctcttctc ctgtcagtaa ccgcaggtgt ccactcccag    60
gttcagctgc agcagctctg agctgtactg atgaagcctg gggcctcagt gaagatatcc    120
tgcaaggcta ctggctacac attcattagg tactggatag agtgggtaaa gaagaggcct    180
ggacatggcc ttgactggat tggagaaatt ttacctggaa gtggaagtcc taactacaat    240
gagaacttca aggtcaaggc cactttcact gtagatactt cctccaacac agcctacatg    300
caactcaaca gcctgacatc tcaggactct gccgtctatt actgtgcaat ttggtacgat    360
ggtaattacc gctctcttat ggactactgg ggtaaggaa cctcagtcac cgtctcctca    420

```

```

<210> SEQ ID NO 27
<211> LENGTH: 131
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 27
Met Lys Leu Pro Val Arg Leu Leu Val Leu Met Phe Trp Ile Pro Ala
1          5          10          15
Ser Ser Ser Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val
20        25        30
Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu
35        40        45
Val Arg Ser Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro
50        55        60
Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser
65        70        75        80
Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
85        90        95
Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys
100       105       110

```

-continued

Ser Gln Ser Thr His Val Pro Tyr Thr Phe Gly Ser Gly Thr Lys Leu
 115 120 125

Glu Ile Lys
 130

<210> SEQ ID NO 28
 <211> LENGTH: 140
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 28

Met Glu Trp Thr Trp Val Phe Leu Phe Leu Leu Ser Val Thr Ala Gly
 1 5 10 15

Val His Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Val Leu Met Lys
 20 25 30

Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe
 35 40 45

Ile Arg Tyr Trp Ile Glu Trp Val Lys Lys Arg Pro Gly His Gly Leu
 50 55 60

Asp Trp Ile Gly Glu Ile Leu Pro Gly Ser Gly Ser Ser Asn Tyr Asn
 65 70 75 80

Glu Asn Phe Lys Val Lys Ala Thr Phe Thr Val Asp Thr Ser Ser Asn
 85 90 95

Thr Ala Tyr Met Gln Leu Asn Ser Leu Thr Ser Gln Asp Ser Ala Val
 100 105 110

Tyr Tyr Cys Ala Ile Trp Tyr Asp Gly Asn Tyr Arg Ser Leu Met Asp
 115 120 125

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
 130 135 140

<210> SEQ ID NO 29
 <211> LENGTH: 381
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 29

atgagtgtgc cactcaggt cctggcattg ctgctgctgt ggcttacaga tgccagatgt 60
 gatatccaga tgactcagtc tccagcctcc ctatctgcat ctgtgggaga aactgtcacc 120
 atcacatgtc gagcaagtgg gaatattcac aattatcttag catgggtatca gcagaaacag 180
 ggaaaatctc ctcagctcct ggtctataat gcaaaaacct tagcgggaagg tgtgccatca 240
 aggttcagtg gcagtggatc aggaacacaa tattctctca agatcaacag cctgcagcct 300
 gaggattttg ggacttatta ctgtcttcat tattacaata ttccgctcac gttcgggtgt 360
 gggaccacgc tggagctgaa a 381

<210> SEQ ID NO 30
 <211> LENGTH: 414
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 30

atgagagtgc tgattctttt gtggctgttc acagcctttc ctggtttcct gtctgatgtg 60

-continued

```

cagcttcagg agtcaggacc tggcctggtg aaaccttctc agtctctgtc cgtcacctgc   120
actgtcactg gctactccat catcagtggg tattactgga actggatccg gcagtttcca   180
ggaaacaaac tggagtggct gggctccata cacaacagtg gtcgcactaa ctacaatcca   240
tctctcaaaa gtcgaatctc tatcagtcga gacacatcca agaaccaatt cttctgcag   300
ctggattctg tgactactga ggacacagcc acatattact gtcacttggg ggacgatggt   360
acctactctg ctatggacta ctgggggtcaa ggaacctcag tcacctctc ctca       414

```

```

<210> SEQ ID NO 31
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

```

```

<400> SEQUENCE: 31

```

```

Met Ser Val Pro Thr Gln Val Leu Ala Leu Leu Leu Trp Leu Thr
1      5      10      15
Asp Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser
20     25     30
Ala Ser Val Gly Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Gly Asn
35     40     45
Ile His Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro
50     55     60
Gln Leu Leu Val Tyr Asn Ala Lys Thr Leu Ala Glu Gly Val Pro Ser
65     70     75     80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn
85     90     95
Ser Leu Gln Pro Glu Asp Phe Gly Thr Tyr Tyr Cys Leu His Tyr Tyr
100    105    110
Asn Ile Pro Leu Thr Phe Gly Ala Gly Thr Thr Leu Glu Leu Lys
115    120    125

```

```

<210> SEQ ID NO 32
<211> LENGTH: 138
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

```

```

<400> SEQUENCE: 32

```

```

Met Arg Val Leu Ile Leu Leu Trp Leu Phe Thr Ala Phe Pro Gly Phe
1      5      10      15
Leu Ser Asp Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro
20     25     30
Ser Gln Ser Leu Ser Val Thr Cys Thr Val Thr Gly Tyr Ser Ile Ile
35     40     45
Ser Gly Tyr Tyr Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu
50     55     60
Glu Trp Leu Gly Ser Ile His Asn Ser Gly Arg Thr Asn Tyr Asn Pro
65     70     75     80
Ser Leu Lys Ser Arg Ile Ser Ile Ser Arg Asp Thr Ser Lys Asn Gln
85     90     95
Phe Phe Leu Gln Leu Asp Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr
100    105    110
Tyr Cys His Leu Gly Asp Asp Gly Thr Tyr Ser Ala Met Asp Tyr Trp

```

-continued

115	120	125	
Gly Gln Gly Thr Ser Val	Thr Val Ser Ser		
130	135		
<p><210> SEQ ID NO 33</p> <p><211> LENGTH: 381</p> <p><212> TYPE: DNA</p> <p><213> ORGANISM: Artificial Sequence</p> <p><220> FEATURE:</p> <p><223> OTHER INFORMATION: Antibody Sequence</p> <p><400> SEQUENCE: 33</p>			
atgaggaccc	ctgctcagtt	tcttggaatc	ttgttgctct ggtttccagg tatcaagtgt 60
gacatcaaga	tgaccacgtc	tccatcttcc	atgtatgcat ctctaggaga gagagtcact 120
atctcttgca	aggcgagtc	ggacattaat	cgctatttaa gctggttcct gcagaaacca 180
gggaaatctc	ctaagaccct	gatctatcgt	acaaacagat tagtagatgg ggtcccatca 240
agggttcagt	gcagtggatc	tggaacaagt	tattctctca ccatcagcag cctggagtat 300
gaagatttgg	gaatttatta	ttgtctacat	tatgctgagt ttctctccac gttcgggtgt 360
gggactaagc	tggaagtga	a	381
<p><210> SEQ ID NO 34</p> <p><211> LENGTH: 414</p> <p><212> TYPE: DNA</p> <p><213> ORGANISM: Artificial Sequence</p> <p><220> FEATURE:</p> <p><223> OTHER INFORMATION: Antibody Sequence</p> <p><400> SEQUENCE: 34</p>			
atgtacttgg	gactgaactg	tgtattcata	gtttttctct taaaaggtgt ccagagtga 60
gtgaaacttg	aggagtctgg	aggaggcttg	gtacaacctg gaggatccat gaaactctcc 120
tgtgttgctc	ctggattcat	tttcagtaac	tactggatgg actggatccg ccagtctcca 180
gagaaggggc	ttgagtgggt	tgctcaaatt	agattgagat ctaataatta tgcgacacat 240
tatgcggagt	ctttgaaagg	gagggtccac	atctcaagag atgattccaa aagtactgtc 300
tacctgcaaa	tgaacagttt	aagaactgaa	gactctggca tttattactg tacgaggact 360
atgattacga	caccagcta	ctggggccaa	ggcaccactc tcacagtctc ctca 414
<p><210> SEQ ID NO 35</p> <p><211> LENGTH: 127</p> <p><212> TYPE: PRT</p> <p><213> ORGANISM: Artificial Sequence</p> <p><220> FEATURE:</p> <p><223> OTHER INFORMATION: Antibody Sequence</p> <p><400> SEQUENCE: 35</p>			
Met Arg Thr Pro Ala Gln Phe Leu Gly Ile Leu Leu Trp Phe Pro			
1	5	10	15
Gly Ile Lys Cys Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr			
20	25	30	
Ala Ser Leu Gly Glu Arg Val Thr Ile Ser Cys Lys Ala Ser Gln Asp			
35	40	45	
Ile Asn Arg Tyr Leu Ser Trp Phe Leu Gln Lys Pro Gly Lys Ser Pro			
50	55	60	
Lys Thr Leu Ile Tyr Arg Thr Asn Arg Leu Val Asp Gly Val Pro Ser			
65	70	75	80
Arg Phe Ser Gly Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser			

-continued

85	90	95
Ser Leu Glu Tyr Glu Asp Leu Gly Ile Tyr Tyr Cys Leu His Tyr Ala		
100	105	110
Glu Phe Pro Pro Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys		
115	120	125

<210> SEQ ID NO 36
 <211> LENGTH: 138
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 36

Met Tyr Leu Gly Leu Asn Cys Val Phe Ile Val Phe Leu Leu Lys Gly	
1	15
Val Gln Ser Glu Val Lys Leu Glu Glu Ser Gly Gly Gly Leu Val Gln	
20	30
Pro Gly Gly Ser Met Lys Leu Ser Cys Val Ala Ser Gly Phe Ile Phe	
35	45
Ser Asn Tyr Trp Met Asp Trp Ile Arg Gln Ser Pro Glu Lys Gly Leu	
50	60
Glu Trp Val Ala Gln Ile Arg Leu Arg Ser Asn Asn Tyr Ala Thr His	
65	80
Tyr Ala Glu Ser Leu Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser	
85	95
Lys Ser Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Ser	
100	110
Gly Ile Tyr Tyr Cys Thr Arg Thr Met Ile Thr Thr Pro Ser Tyr Trp	
115	125
Gly Gln Gly Thr Thr Leu Thr Val Ser Ser	
130	135

<210> SEQ ID NO 37
 <211> LENGTH: 381
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 37

atgagtgtgc ccactcaggt cctggcattg ctgctgctgt ggcttacaga tgccagatgt	60
gatatccaga tgactcagtc tccagcctcc ctatctgcat ctgtgggaga aactgtcacc	120
atcacatgtc gagcaagtgg gaatattcac aattatttag catggatatca gcagaaacag	180
ggaaaatctc ctcagctcct ggtctataat acaaaatcct tggcggaagg tgtgccatca	240
aggttcagtg gcagtggatc aggaacacaa tattctctca agatctacag cctgcagcct	300
gcggattttg gggcttatta ctgtcttcat tattataata ctccgctcac ttccggtgct	360
gggaccaagc tagagctgag a	381

<210> SEQ ID NO 38
 <211> LENGTH: 414
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 38

-continued

```

atgagagtgc tgattctttt gtggctgttc acagcctttc ctggatcct gtctgatgtg      60
cagcttcagg agtcaggacc tggcctgggtg aaaccttctc agtctctgtc cgtcacctgc      120
actgtcactg gcttctccat caccagtggg tattactgga actggatccg gcagtttcca      180
ggaaacaaac tggagtggat gggctacata cacaacagtg gtcgcactaa ctacaatcca      240
tctctcaaaa gtcgaatctc tatcactcga gacacatcca aaaaccagtt cttctgcag      300
ttgagtctcg tgactaatgc ggacacagcc acatattact gtcacttggg ggacgatggg      360
acctcctatg ctatggacta ctgggggtcaa ggaacctcag tcaccgtctc ctca      414

```

```

<210> SEQ ID NO 39
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

```

```

<400> SEQUENCE: 39

```

```

Met Ser Val Pro Thr Gln Val Leu Ala Leu Leu Leu Trp Leu Thr
 1              5              10              15
Asp Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser
      20              25              30
Ala Ser Val Gly Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Gly Asn
      35              40              45
Ile His Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro
      50              55              60
Gln Leu Leu Val Tyr Asn Thr Lys Ser Leu Ala Glu Gly Val Pro Ser
      65              70              75              80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Tyr
      85              90              95
Ser Leu Gln Pro Ala Asp Phe Gly Ala Tyr Tyr Cys Leu His Tyr Tyr
      100             105             110
Asn Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Arg
      115             120             125

```

```

<210> SEQ ID NO 40
<211> LENGTH: 138
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

```

```

<400> SEQUENCE: 40

```

```

Met Arg Val Leu Ile Leu Leu Trp Leu Phe Thr Ala Phe Pro Gly Ile
 1              5              10              15
Leu Ser Asp Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro
      20              25              30
Ser Gln Ser Leu Ser Val Thr Cys Thr Val Thr Gly Phe Ser Ile Thr
      35              40              45
Ser Gly Tyr Tyr Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu
      50              55              60
Glu Trp Met Gly Tyr Ile His Asn Ser Gly Arg Thr Asn Tyr Asn Pro
      65              70              75              80
Ser Leu Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln
      85              90              95
Phe Phe Leu Gln Leu Ser Ser Val Thr Asn Ala Asp Thr Ala Thr Tyr
      100             105             110

```

-continued

Tyr Cys His Leu Gly Asp Asp Gly Thr Ser Tyr Ala Met Asp Tyr Trp
 115 120 125

Gly Gln Gly Thr Ser Val Thr Val Ser Ser
 130 135

<210> SEQ ID NO 41
 <211> LENGTH: 384
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 41

atggattttc aggtgcagat tttcagcttc ctgctaataca gtgcctcagt catactgtcc	60
agaggacaaa ttgttctcac ccagtctcca gcaatcatgt ctgcatctct gggggaggag	120
atcacccctaa cctgcagtg cagctcgagt gtaaattaca tgcactggta ccagcagaag	180
tcaggcaact ctcccaaact ctgtatttat agcacatcca acctggcttc tggagtcct	240
tctcgcttca gtggcagtg gtctgggacc ttttattctc tcacaatcag cagtgtggag	300
gctgaagatg ctgccgatta ttactgccat cagtggagta gttatccgta cacgttcgga	360
ggggggacca agctggaaat aaaa	384

<210> SEQ ID NO 42
 <211> LENGTH: 408
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 42

atggaatgga gttgatatt tctctttctc ctgtcaggaa ctgcaggtgt ccactctgag	60
gtccagttgc agcagtctgg acctgagctg gtaaagcctg gggcttcagt gaagatgtcc	120
tgcaaggctt ctggatacac attcactaac tatgttattt actgggtgaa gcagaagcct	180
gggcagggcc ttgagtggat tggatatatt aatccttaca atgatggtac taagtacaat	240
gagaagtcca aaggcaaggc cacactgact gcagacaaat cctccagcac agcctacatg	300
gagctcagta gcctgacctc tgaggactct gcggtctatt actgtgcctg taacttctc	360
tatgctatgg actactgggg tcaaggaacc tcagtcaccg tctctca	408

<210> SEQ ID NO 43
 <211> LENGTH: 128
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 43

Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
 1 5 10 15

Val Ile Leu Ser Arg Gly Gln Ile Val Leu Thr Gln Ser Pro Ala Ile
 20 25 30

Met Ser Ala Ser Leu Gly Glu Glu Ile Thr Leu Thr Cys Ser Ala Ser
 35 40 45

Ser Ser Val Asn Tyr Met His Trp Tyr Gln Gln Lys Ser Gly Thr Ser
 50 55 60

Pro Lys Leu Leu Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Val Pro
 65 70 75 80

-continued

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Phe Tyr Ser Leu Thr Ile
85 90 95

Ser Ser Val Glu Ala Glu Asp Ala Ala Asp Tyr Tyr Cys His Gln Trp
100 105 110

Ser Ser Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
115 120 125

<210> SEQ ID NO 44
<211> LENGTH: 136
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 44

Met Glu Trp Ser Trp Ile Phe Leu Phe Leu Leu Ser Gly Thr Ala Gly
1 5 10 15

Val His Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys
20 25 30

Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

Thr Asn Tyr Val Ile Tyr Trp Val Lys Gln Lys Pro Gly Gln Gly Leu
50 55 60

Glu Trp Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn
65 70 75 80

Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser
85 90 95

Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
100 105 110

Tyr Tyr Cys Ala Cys Asn Phe Leu Tyr Ala Met Asp Tyr Trp Gly Gln
115 120 125

Gly Thr Ser Val Thr Val Ser Ser
130 135

<210> SEQ ID NO 45
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 45

atggagtcac agattccaggc atttgtattc gtgtttctct ggttgtctgg tgttgacgga 60

gacattgtga tgaccagtc tcacaaattc atgtccacat cagtaggaga cagggtcagc 120

atcacctgca aggccagtca ggatgtgaat actgctgtag cctgggtatca aaaaaatta 180

ggacaatctc ctaaaactgct gatttattgg gcatccaccc ggcacactgg agtccctgat 240

cgcttcacag gcagtggatc tgggacagat tatactctca ccatcagcag tgtgcaggct 300

gaagacctgg cactttatta ctgtcagcaa cattatagca ctccgtacac gttcggaggg 360

gggaccaagc tggaaataaa a 381

<210> SEQ ID NO 46
<211> LENGTH: 411
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 46

-continued

```

atgggatgga gctatatcat cctctttttg gtagcaacag ctacagatgt ccactcccag      60
gtccaactgc agcagcctgg ggctgaactg gtgacgcctg gggcttcagt gaagctgtcc      120
tgcaaggcct ctggctacac cttcaccagc tactggatgc actgggtgaa gcagaggcct      180
ggacaaggcc ttgagtggat tggagagatt aatcctggca acggtcgtac taactacaat      240
gataatttca tgatcagggc cactactgact gtggacaaat cctccagcac agcctacatg      300
caactcagca gcctgacatc tgaggactct gcggtctatt actgtgcaag aagcctctac      360
ggtaccctct ttgcttctcg gggccaaggg actctgggtc ctgtctctgc a              411

```

```

<210> SEQ ID NO 47
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

```

```

<400> SEQUENCE: 47

```

```

Met Glu Ser Gln Ile Gln Ala Phe Val Phe Val Phe Leu Trp Leu Ser
 1              5              10              15
Gly Val Asp Gly Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser
          20              25              30
Thr Ser Val Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp
          35              40              45
Val Asn Thr Ala Val Ala Trp Tyr Gln Lys Lys Leu Gly Gln Ser Pro
          50              55              60
Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp
          65              70              75              80
Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser
          85              90              95
Ser Val Gln Ala Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr
          100             105             110
Ser Thr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
          115             120             125

```

```

<210> SEQ ID NO 48
<211> LENGTH: 137
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

```

```

<400> SEQUENCE: 48

```

```

Met Gly Trp Ser Tyr Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Asp
 1              5              10              15
Val His Ser Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Thr
          20              25              30
Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe
          35              40              45
Thr Ser Tyr Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu
          50              55              60
Glu Trp Ile Gly Glu Ile Asn Pro Gly Asn Gly Arg Thr Asn Tyr Asn
          65              70              75              80
Asp Asn Phe Met Ile Arg Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
          85              90              95
Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
          100             105             110

```

-continued

Tyr Tyr Cys Ala Arg Ser Leu Tyr Gly Thr Leu Phe Ala Ser Trp Gly
 115 120 125

Gln Gly Thr Leu Val Thr Val Ser Ala
 130 135

<210> SEQ ID NO 49
 <211> LENGTH: 393
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 49

atggagacag acacactcct gctatgggtg ctgctgctct gggttccagg ttccactggt 60
 gacattgtac tgacacagtc tctgtttcc ttaactatct ctctgggccca gagggccacc 120
 atctcatgca gggccagcca aagtgtcagt gcatctagct atagttatat gcactggtag 180
 caacagaaag caggacagcc acccaaactc ctcacaaagt atgcatccaa cctagaatct 240
 ggggtccctg ccagggttcag tggcagtggt tctgggacag acttcacct caacatccat 300
 cctgtggagg aggcggatag tgcaacatac tactgtcaac acaattggga gggtcctccg 360
 acgttcggtg gaggcaccaa gctggaatc aag 393

<210> SEQ ID NO 50
 <211> LENGTH: 423
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 50

atggactcca ggctcaatct agttttcctt gtccttggtt taaaagggtg ccagtgtgat 60
 gtgcagttgg tggagtctgg gggaggctta gtgcagcctg gaggggtccc gaaactctcc 120
 tgtgcagcct ctggattcac gttcagtagc tttggaatgc actggggttcg tcaggctcca 180
 gagaaggggc tggaatgggt cgcataatct agtagtgga gtagtaccat ctactataga 240
 gacacagtga agggccgatt caccatctcc agagacaatc ccaagaacac cctgttctcg 300
 caaatgacca gtctaaggtc tgaggacacg gccatgtatt actgtgcaag agggggggta 360
 gtagtttcga aagatggaaa ctttgactac tggggccaag gcaccactct cgcagtctcc 420
 tca 423

<210> SEQ ID NO 51
 <211> LENGTH: 131
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 51

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
 1 5 10 15

Gly Ser Thr Gly Asp Ile Val Leu Thr Gln Ser Pro Val Ser Leu Thr
 20 25 30

Ile Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Gln Ser
 35 40 45

Val Ser Ala Ser Ser Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Ala
 50 55 60

-continued

Gly Gln Pro Pro Lys Leu Leu Ile Lys Tyr Ala Ser Asn Leu Glu Ser
65 70 75 80

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
85 90 95

Leu Asn Ile His Pro Val Glu Glu Ala Asp Thr Ala Thr Tyr Tyr Cys
100 105 110

Gln His Asn Trp Glu Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu
115 120 125

Glu Ile Lys
130

<210> SEQ ID NO 52
 <211> LENGTH: 141
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 52

Met Asp Ser Arg Leu Asn Leu Val Phe Leu Val Leu Val Leu Lys Gly
1 5 10 15

Val Gln Cys Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

Pro Gly Gly Ser Arg Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Ser Phe Gly Met His Trp Val Arg Gln Ala Pro Glu Lys Gly Leu
50 55 60

Glu Trp Val Ala Tyr Ile Ser Ser Gly Ser Ser Thr Ile Tyr Tyr Arg
65 70 75 80

Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Pro Lys Asn
85 90 95

Thr Leu Phe Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met
100 105 110

Tyr Tyr Cys Ala Arg Gly Gly Val Val Val Ser Lys Asp Gly Asn Phe
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Ala Val Ser Ser
130 135 140

<210> SEQ ID NO 53
 <211> LENGTH: 381
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 53

atgatgtcct ctgctcagtt ccttggyctc ctgttgctct gttttcaagg taccagatgt 60

gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagagtcacc 120

aycagttgca gtgcaagtca gggcattagc aattatttaa actggtatca gcagaaacca 180

gatggaactg ttaaactcct gatctattac acatcaagtt tacactcagg agtcccatca 240

aggttcagtg gcagtggggtc tgggacagat tattctctca ccatcagcaa cctggaacct 300

gaagatattg ccacttacta ttgtcagcag tatagtaagc ttccgtacac gttcggaggg 360

gggaccaaac tggaaataaa a 381

<210> SEQ ID NO 54
 <211> LENGTH: 399

-continued

```

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

<400> SEQUENCE: 54

atggaaaggc actggatctt tctcttctg ttgtcagtaa ctgcagggtg ccactcccag      60
gtccaactgc agcagctctgc ggctgaactg gtaagacctg gggcctcagt gaagatgtcc      120
tgcaagactt ctggctacat ctctactagc gaccggatgc actgggtaaa acagaggcct      180
ggacagggtc tggagtggat tggatacatt attctagaa atttttatac taaatacaat      240
cagaaattca aggacaaggc cacattgact gcagacacat cctccaatac agcctacatg      300
cagttgagca gcctgacatc tgaagactct gcagtctatt actgtgtgaa atctgacggg      360
gcctactggg gccaaaggc acactctaca gtctctca                                399

```

```

<210> SEQ ID NO 55
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (41)..(41)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 55

```

```

Met Met Ser Ser Ala Gln Phe Leu Gly Leu Leu Leu Cys Phe Gln
 1          5          10          15

Gly Thr Arg Cys Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser
 20          25          30

Ala Ser Leu Gly Asp Arg Val Thr Xaa Ser Cys Ser Ala Ser Gln Gly
 35          40          45

Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val
 50          55          60

Lys Leu Leu Ile Tyr Tyr Thr Ser Ser Leu His Ser Gly Val Pro Ser
 65          70          75          80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser
 85          90          95

Asn Leu Glu Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser
100          105          110

Lys Leu Pro Tyr Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys
115          120          125

```

```

<210> SEQ ID NO 56
<211> LENGTH: 133
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody Sequence

```

```

<400> SEQUENCE: 56

Met Glu Arg His Trp Ile Phe Leu Phe Leu Leu Ser Val Thr Ala Gly
 1          5          10          15

Val His Ser Gln Val Gln Leu Gln Gln Ser Ala Ala Glu Leu Val Arg
 20          25          30

Pro Gly Ala Ser Val Lys Met Ser Cys Lys Thr Ser Gly Tyr Ile Phe
 35          40          45

Thr Ser Asp Arg Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu

```

50					55					60					
Glu	Trp	Ile	Gly	Tyr	Ile	Ile	Pro	Arg	Asn	Phe	Tyr	Thr	Lys	Tyr	Asn
65					70					75					80
Gln	Lys	Phe	Lys	Asp	Lys	Ala	Thr	Leu	Thr	Ala	Asp	Thr	Ser	Ser	Asn
			85					90					95		
Thr	Ala	Tyr	Met	Gln	Leu	Ser	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val
			100					105					110		
Tyr	Tyr	Cys	Val	Lys	Ser	Asp	Gly	Ala	Tyr	Trp	Gly	Gln	Gly	Thr	Thr
		115					120					125			
Leu	Thr	Val	Ser	Ser											
130															

1. An isolated antibody or a binding fragment thereof, which specifically binds to paliperidone and which said isolated antibody or binding fragment thereof is selected from the group of amino acid sequences consisting of:

- a) the isolated antibody or the binding fragment thereof comprising a heavy chain variable region, and a light chain variable region wherein said light chain variable region comprising an amino acid sequence of SEQ ID NO:3 or SEQ ID NO:7;
- b) the isolated antibody or the binding fragment thereof comprising a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:4 or SEQ ID NO:8, and a light chain variable region;
- c) the isolated antibody or the binding fragment thereof comprising a light chain variable region having an amino acid sequence of SEQ ID NO:3 and a heavy chain variable region having an amino acid sequence of SEQ ID NO:4; or
- d) the isolated antibody or the binding fragment thereof comprising a light chain variable region having an amino acid sequence of SEQ ID NO:7 and a heavy chain variable region having an amino acid sequence of SEQ ID NO:8.

2. The isolated antibody of claim 1, wherein the antibody comprises the light chain variable region having the amino acid sequence SEQ ID NO:3 and the heavy chain variable region having the amino acid sequence SEQ ID NO:4.

3. The isolated antibody of claim 1, wherein the antibody comprises the light chain variable region having the amino acid sequence SEQ ID NO:7 and the heavy chain variable region having the amino acid sequence SEQ ID NO:8.

4. The isolated antibody of claim 1, wherein the antibody comprises:

- a) a light chain CDR1 sequence comprising amino acid residues 44 to 60 of SEQ ID NO:3;
- b) a light chain CDR2 sequence comprising amino acid residues 76 to 82 of SEQ ID NO:3;
- c) a light chain CDR3 sequence comprising amino acid residues 115 to 123 of SEQ ID NO:3;
- d) a heavy chain CDR1 sequence comprising amino acid residues 45 to 54 of SEQ ID NO:4;
- e) a heavy chain CDR2 sequence comprising amino acid residues 69 to 85 of SEQ ID NO:4; and
- f) a heavy chain CDR3 sequence comprising amino acid residues 118 to 122 of SEQ ID NO:4.

5. The isolated antibody of claim 1, wherein the antibody comprises:

- a) a light chain CDR1 sequence comprising amino acid residues 44 to 60 of SEQ ID NO:7;
- b) a light chain CDR2 sequence comprising amino acid residues 76 to 82 of SEQ ID NO:7;
- c) a light chain CDR3 sequence comprising amino acid residues 115 to 123 of SEQ ID NO:7;
- d) a heavy chain CDR1 sequence comprising amino acid residues 45 to 54 of SEQ ID NO:8;
- e) a heavy chain CDR2 sequence comprising amino acid residues 69 to 85 of SEQ ID NO:8; and
- f) a heavy chain CDR3 sequence comprising amino acid residues 118 to 122 of SEQ ID NO:8.

6. The isolated antibody of claim 1, wherein the antibody fragment is selected from the group of fragments consisting of Fv, F(ab'), F(ab')₂, scFv, minibody and diabody fragments.

7. The isolated antibody of claim 1, wherein the antibody is a monoclonal antibody.

8. An assay kit comprising the isolated antibody of claim 1.

9. An assay device comprising the isolated antibody of claim 1.

10. The assay device of claim 9 wherein the device is a lateral flow assay device.

11. A method of detecting paliperidone in a sample, the method comprising:

- (i) contacting a sample with the isolated antibody of claim 1 labeled with a detectable marker, wherein the labeled antibody and paliperidone present in the sample form a labeled complex; and
- (ii) detecting the labeled complex so as to detect paliperidone in the sample.

12. A competitive immunoassay method for detecting paliperidone in a sample, the method comprising:

- (i) contacting a sample with the isolated antibody of claim 1, and with paliperidone or a competitive binding partner thereof, wherein one of the isolated antibody and the paliperidone or competitive binding partner thereof is labeled with a detectable marker, and wherein sample paliperidone competes with the paliperidone or competitive binding partner thereof for binding to the isolated antibody; and
- (ii) detecting the label so as to detect sample paliperidone.

13. The method of claim 12 wherein the paliperidone or competitive binding partner thereof is labeled with the detectable marker.

14. The method of claim 12 wherein the antibody is labeled with a detectable marker.

75

15. The method of claim **12** wherein the immunoassay is performed on a lateral flow assay device and the sample is applied to the device.

16. The method of claim **11** or **12**, further comprising detecting the presence of one or more analytes in addition to paliperidone. 5

17. The method of claim **16** wherein the one or more analytes are anti-psychotic drugs other than paliperidone.

18. The method of claim **17** wherein the anti-psychotic drugs other than paliperidone are selected from the group consisting of: risperidone, quetiapine, olanzapine, aripiprazole, and metabolites thereof. 10

* * * * *

76